FILE 'REGISTRY' ENTERED AT 15:26:36 ON 17 DEC 2004
E OSTEOGENIC PROTEIN/CN
L1 3 S E4 OR E15-16

(FILE 'CAPLUS' ENTERED AT 15:35:12 ON 17 DEC 2004)
L1 3 SEA FILE=REGISTRY ABB=ON PLU=ON "OSTEOGENIC PROTEIN 1 (HUMAN)"/CN OR ("OSTEOGENIC PROTEIN-1 (HUMAN CLONE US6407060B1-SEQID5)"/CN OR "OSTEOGENIC PROTEIN-1 (MOUSE)"/CN)
L7 1167 SEA FILE=CAPLUS ABB=ON PLU=ON L1 OR (OP OR OSTEOGEN? PROTEIN)(W)(1 OR I) OR (OPI OR OP1)(S)OSTEOGEN? OR BMP7 OR (BONE MORPHOGEN? PROTEIN OR BMP)(W)7
L8 44 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND TISSUE(S)(DISEAS? OR DISORDER)
L9 15 SEA FILE=CAPLUS ABB=ON PLU=ON L8 AND (DETERM? OR DETECT? OR DET## OR SCREEN? OR DIAGNOS? OR PREDETERM? OR MEAS? OR QUANT?)

L9 ANSWER 1 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 25 Aug 2004
ACCESSION NUMBER: 2004:690993 CAPLUS
DOCUMENT NUMBER: 141:311759
TITLE: Differential gene expression in ovarian carcinoma: Identification of potential biomarkers
AUTHOR(S): Hibbs, Kathleen; Skubitz, Keith M.; Pambuccian, Stefan E.; Casey, Rachael C.; Burleson, Kathryn M.; Oegema, Theodore R., Jr.; Thiele, Jeannine J.; Grindle, Suzanne M.; Bliss, Robin L.; Skubitz, Amy P. N.
CORPORATE SOURCE: Departments of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA
SOURCE: American Journal of Pathology (2004), 165(2), 397-414
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ovarian cancer remains the fifth leading cause of cancer death for women in the United States. In this study, the gene expression of 20 ovarian carcinomas, 17 ovarian carcinomas metastatic to the omentum, and 50 normal ovaries was **determined** by Gene Logic Inc. using Affymetrix GeneChip HU_95 arrays containing .apprx.12,000 known genes. Differences in gene expression were **quantified** as fold changes in gene expression in ovarian carcinomas compared to normal ovaries and ovarian carcinoma metastases. Genes up-regulated in ovarian carcinoma **tissue** samples compared to more than 300 other normal and **diseased** **tissue** samples were identified. Seven genes were selected for further **screening** by immunohistochem. to **determine** the presence and localization of the proteins. These seven genes were: the β8 integrin subunit, **bone morphogenetic** **protein-7**, claudin-4, collagen type IX α2, cellular retinoic acid binding protein-1, forkhead box J1, and S100 calcium-binding protein A1. Statistical analyses showed that the β8 integrin subunit, claudin-4, and S100A1 provided the best distinction between ovarian carcinoma and normal ovary tissues, and may serve as the best candidate tumor markers among the seven genes studied. These results suggest that further exploration into other up-regulated genes may identify novel **diagnostic**, therapeutic, and/or prognostic biomarkers in ovarian carcinoma.
REFERENCE COUNT: 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 15 Jul 2004
ACCESSION NUMBER: 2004:565114 CAPLUS
DOCUMENT NUMBER: 141:117155
TITLE: Methods of **diagnosing**, preventing, and treating early onset of pulmonary hypertension
INVENTOR(S): Stewart, Duncan J.; Babaei, Saeid; Courtman, David
PATENT ASSIGNEE(S): Northern Therapeutics Inc., Can.
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058293	A1	20040715	WO 2003-CA2007	20031224

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-435861P P 20021224
AB Early onset of pulmonary disorders such as pulmonary hypertension are treated or prevented by administration of an apoptosis inhibitor or a survival factor. Early onset of such **disorders** may be **diagnosed** by assessing apoptosis in lung **tissue**.

L9 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 16 May 2003
ACCESSION NUMBER: 2003:377088 CAPLUS
DOCUMENT NUMBER: 138:380384
TITLE: Method and device for **detecting** and monitoring alcoholism and related diseases using microarrays
INVENTOR(S): Harris, Adron; Mayfield, Dayne R.; Lewohl, Jo; Dodd, Peter R.
PATENT ASSIGNEE(S): University of Texas System, USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003040414	A1	20030515	WO 2002-US35902	20021108

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003104457	A1	20030605	US 2002-291247	20021107
EP 1451374	A1	20040901	EP 2002-802883	20021108

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.: US 2001-338270P P 20011108
WO 2002-US35902 W 20021108

AB A device and method for **detecting**, **diagnosing**, and or monitoring alcoholism and related disease states is disclosed. The device includes a substrate and one or more alcoholism-specific nucleic acids attached to the substrate. The substrate is contacted by a sample collected from a person with alcoholism or alc. abuse or an alc. related disease state, wherein contact occurs under pre-selected binding conditions that provides information that can be collected and recorded by a computer.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 10 Jan 2003
ACCESSION NUMBER: 2003:23431 CAPLUS
DOCUMENT NUMBER: 138:78566
TITLE: **Quantitative** in vitro bone induction assay
INVENTOR(S): Wironen, John F.; Jaw, Rebecca
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 30 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003008328	A1	20030109	US 2001-897728	20010703
WO 2003004990	A2	20030116	WO 2002-US21026	20020703
WO 2003004990	A3	20031127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-897728 A 20010703

AB An in vitro assay for **quantifying** the osteogenic capacity of bone implants involves in vitro isolation and **quantitation** of specific osteogenic factors. The method disclosed permits direct **measurement** of the osteogenic capacity of an implant to allow greater predictability of the degree to which new bone will grow in a given area. The method eliminates the need to practice the traditional technique of implanting material into a test animal and subsequently sacrificing the animal to assess bone growth associated with the implant. Since the present method does not involve animal testing, it is an extremely reproducible, rapid, and accurate method for predicting whether an implanted composition or material will induce bone growth without the need for in vivo assays. For example, the chondrogenic capacity of a bone implant was **measured** in vitro by releasing chondrogenic factors from the implant (e.g., BMP-2 and BMP-4), in vitro **measuring** the concns. of chondrogenic factors present, and exposing tissue containing mesenchymal or other undifferentiated cells to a composition of these proteins.

The degree of development of chondroblasts and chondrocytes in vitro is used to confirm the chondrogenic capacity of the implant predicted by the present in vitro assay method. The degree of differentiation can be manipulated to reach a desired result by altering the specific concns. of chondrogenic factors included in a given implant.

L9 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 03 Jan 2003
ACCESSION NUMBER: 2003:5353 CAPLUS
DOCUMENT NUMBER: 138:52349
TITLE: Multipotent stem cells from peripheral tissues and uses thereof
INVENTOR(S): Toma, Jean; Akhavan, Mahnaz; Fernandes, Karl J. L.; Fortier, Mathieu; Miller, Freda
PATENT ASSIGNEE(S): Can.
SOURCE: U.S. Pat. Appl. Publ., 55 pp., Cont.-in-part of U.S. Ser. No. 991,480.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003003574	A1	20030102	US 2002-99539	20020315
US 6787355	B1	20040907	US 2000-670049	20000925
WO 2001053461	A1	20010726	WO 2001-CA47	20010124

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002016002	A1	20020207	US 2001-916639	20010726
US 2002123143	A1	20020905	US 2001-991480	20011109
WO 2003010243	A2	20030206	WO 2002-CA1130	20020726
WO 2003010243	A3	20030731		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1414947	A2	20040506	EP 2002-748521	20020726

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

PRIORITY APPLN. INFO.:	US 2000-490422	B2 20000124
	US 2000-670049	A2 20000925
	WO 2001-CA47	A2 20010124
	US 2001-916639	A2 20010726
	US 2001-991480	A2 20011109
	US 1996-24590P	P 19960826
	US 1996-24456P	P 19960827
	US 1997-920272	A2 19970822
	US 2002-99539	A 20020315
	WO 2002-CA1130	W 20020726

AB This invention relates to multipotent stem cells, purified from the peripheral tissue of mammals, and capable of differentiating into neural and non-neural cell types. These stem cells provide an accessible source for autologous transplantation into CNS, PNS, and other damaged tissues.

L9 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 08 Sep 2002
ACCESSION NUMBER: 2002:676308 CAPLUS
DOCUMENT NUMBER: 137:181946
TITLE: Methods of using bone morphogenic proteins as biomarkers for **determining** cartilage degeneration and aging
INVENTOR(S): Chubinskaya, Susanna; Rueger, David C.; Kuettner, Klaus E.
PATENT ASSIGNEE(S): Stryker Corporation, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068962	A2	20020906	WO 2002-US5551	20020220
WO 2002068962	A3	20031127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2438757	AA	20020906	CA 2002-2438757	20020220
US 2002192679	A1	20021219	US 2002-81163	20020220
EP 1390757	A2	20040225	EP 2002-706405	20020220

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:	US 2001-270528P	P	20010221
	US 2001-348111P	P	20011109
	WO 2002-US5551	W	20020220

AB Methods are provided for **determining** cartilage degeneration or regeneration in a joint tissue in a patient by **measuring** levels of **osteogenic protein-1** (**OP-1**) protein and/or mRNA in synovial fluid or joint tissue. The methods according to the invention are useful for **detecting**, **diagnosing**, predicting, **determining** a predisposition for, or monitoring joint **tissue** degeneration and regeneration in a patient including inflammatory joint **disease** or age-related **disorders**.

L9 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 15 Nov 2001
ACCESSION NUMBER: 2001:828415 CAPLUS
DOCUMENT NUMBER: 137:89412
TITLE: **Detection** of variations in the DNA methylation profile of genes in the **determining** the risk of disease
INVENTOR(S): Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander
PATENT ASSIGNEE(S): Epigenomics A.-G., Germany
SOURCE: PCT Int. Appl., 636 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 68
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077373	A2	20011018	WO 2001-XA1486	20010406

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG

DE 10019058	A1	20011220	DE 2000-10019058	20000406
WO 2001077373	A2	20011018	WO 2001-DE1486	20010406

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,
SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1274865	A2	20030115	EP 2001-953936	20010406
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003531589	T2	20031028	JP 2001-575634	20010406
EP 1360319	A2	20031112	EP 2001-955278	20010406
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004067491	A1	20040408	US 2003-240454	20030311
US 2003162194	A1	20030828	US 2003-240452	20030414
JP 2004008217	A2	20040115	JP 2003-160375	20030605
US 2004023279	A1	20040205	US 2003-455212	20030605
PRIORITY APPLN. INFO.:			DE 2000-10019058 A	20000406
			WO 2001-DE1486 W	20010406
			DE 2000-10019173 A	20000407
			DE 2000-10032529 A	20000630
			DE 2000-10043826 A	20000901
			WO 2001-EP3969 W	20010406
			WO 2001-EP4016 W	20010406
			EP 2002-90203 A	20020605

AB The invention relates to an oligonucleotide kit as probe for the **detection** of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for **determining** the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for **detg** . the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such **diseases** may be: undesired pharmaceutical side-effects; cancerous **diseases**; CNS dysfunctions, injuries or **diseases**; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic **disorders** and personality **disorders**; dementia and/or associated syndromes; cardiovascular **disease**, dysfunction and damage; dysfunction, damage or **disease** of the gastrointestinal tract; dysfunction, damage or **disease** of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or **disease** of the body as an abnormal development process; dysfunction, damage or **disease** of the skin, muscle, connective **tissue** or bones; endocrine and metabolic dysfunction, damage or **disease**; headaches or sexual dysfunction. This abstract record is one of several records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.

L9 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Aug 2000
ACCESSION NUMBER: 2000:535261 CAPLUS
DOCUMENT NUMBER: 133:132131
TITLE: Methods and compositions for the differentiation of

human preadipocytes into adipocytes
INVENTOR(S): Halvorsen, Yuan-Di Chang; Wilkison, William O.
PATENT ASSIGNEE(S): Zen-Bio, Inc., USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000044882	A2	20000803	WO 2000-US2208	20000128
WO 2000044882	A3	20010809		
W: CN, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6153432	A	20001128	US 1999-240029	19990129
PRIORITY APPLN. INFO.:			US 1999-240029 A	19990129

AB The present invention provides methods and compns. for the consistent and **quant.** differentiation of human preadipocytes isolated from adipose tissue into adipocytes bearing biochem., genetic, and physiol. characteristics similar to that observed in isolated primary adipocytes. The methods of the invention comprise incubating isolated human preadipocytes, plated at least about 25,000 cells/cm2, in a medium containing, glucose, a cAMP inducer such as isobutylmethylxanthine or forskolin, a glucocorticoid or glucocorticoid analog, insulin or an insulin analog and a PPARγ agonist or a RXR agonist. Also provided are methods for preparing three dimensional biomatrices containing adipocytes differentiated by the methods of the invention. The compns. of the invention include human adipocytes differentiated by the methods of the invention, three-dimensional matrixes of adipocytes, and transfected adipocytes. The methods and compns. have use in the drug discovery of compds. having relevance to the **disease** states of diabetes, obesity, and cardiovascular **disease** and in the studies of these **diseases**, and in the grafting of fat **tissue**.

L9 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 03 Aug 2000
ACCESSION NUMBER: 2000:531604 CAPLUS
DOCUMENT NUMBER: 133:149138
TITLE: Antibodies specific for growth differentiation factor-8 and methods of using same
INVENTOR(S): Lee, Se-Jin; McPherron, Alexandra C.
PATENT ASSIGNEE(S): The Johns Hopkins University School of Medicine, USA
SOURCE: U.S., 45 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 6096506	A	20000801	US 1998-177860	19981023
US 6500664	B1	20021231	US 2000-629938	20000801
US 2003120058	A1	20030626	US 2002-335483	20021231
PRIORITY APPLN. INFO.:			US 1993-33923	B2 19930319
			WO 1994-US3019	W 19940318
			US 1995-525596	A3 19951026
			US 1998-177860	A1 19981023
			US 2000-629938	A1 20000801

AB Growth differentiation factor-8 (GDF-8) is disclosed along with its polynucleotide sequence and amino acid sequence. Also disclosed are **diagnostic** and therapeutic methods of using the GDF-8 polypeptide and polynucleotide sequences. The antibodies may be polyclonal or monoclonal antibodies and are useful for treating cell proliferative **disorders** of muscle, nerve and adipose **tissue**.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 10 Mar 2000
ACCESSION NUMBER: 2000:161549 CAPLUS
DOCUMENT NUMBER: 132:177747
TITLE: Predictive assessment of certain skeletal disorders
INVENTOR(S): Findlay, David; Fazzalari, Nicola; Kuliwaba, Julia; Forwood, Mark
PATENT ASSIGNEE(S): Medvet Science Pty Ltd., Australia
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000013024	A1	20000309	WO 1999-AU697	19990826
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9957209	A1	20000321	AU 1999-57209	19990826
PRIORITY APPLN. INFO.:			AU 1998-5473	A 19980826
			WO 1999-AU697	W 19990826

AB A method of predicting or **diagnosing** a skeletal disorder in an individual. The method including the steps of taking a sample of body **tissue** or body fluid, **measuring** or estimating the level of at least one regulator or marker of bone remodeling in the sample, and comparing the level to a standard to **determine** whether the level of the regulator or marker falls within a range indicative of a potential of the individual to progress to exhibit overt symptoms of the skeletal **disorder**. Suitable markers or regulators include IL-1α, IL-1β, IL-6 and its soluble and cell membrane receptor, IL-11 and its

receptor, IL-17 and its receptor, M-CSF, ODF, RANK, TRAIL and CTR, IL-18, OPG, BMP2, BMP6, **BMP7**, TGFβ1, TGFβ2, TGFβ3, IGFI, alkaline phosphatases, OCN, and fragments of type I collagen.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 17 Dec 1999
ACCESSION NUMBER: 1999:795994 CAPLUS
DOCUMENT NUMBER: 132:31744
TITLE: Gene probes used for genetic profiling in healthcare **screening** and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Ltd., UK
SOURCE: PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964627	A2	19991216	WO 1999-GB1780	19990604

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
GB 1998-12099	A	19980606
GB 1998-13291	A	19980620
GB 1998-13611	A	19980624
GB 1998-13835	A	19980627
GB 1998-14110	A	19980701
GB 1998-14580	A	19980707
GB 1998-15438	A	19980716
GB 1998-15574	A	19980718
GB 1998-15576	A	19980718
GB 1998-16085	A	19980724
GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable

the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the number of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide critical clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic" profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L9 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 17 Dec 1999
ACCESSION NUMBER: 1999:795993 CAPLUS
DOCUMENT NUMBER: 132:31743
TITLE: Gene probes used for genetic profiling in healthcare **screening** and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Limited, UK
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964626	A2	19991216	WO 1999-GB1779	19990604
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2330929	AA	19991216	CA 1999-2330929	19990604
AU 9941586	A1	19991230	AU 1999-41586	19990604
AU 766544	B2	20031016		
AU 9941587	A1	19991230	AU 1999-41587	19990604
GB 2339200	A1	20000119	GB 1999-12914	19990604
GB 2339200	B2	20010912		
EP 1084273	A1	20010321	EP 1999-925207	19990604

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2003528564	T2	20030930	JP 2000-553616	19990604
US 2003198970	A1	20031023	US 2002-206568	20020729
PRIORITY APPLN. INFO.:			GB 1998-12098 A	19980606
			GB 1998-28289 A	19981223
			GB 1998-16086 A	19980724
			GB 1998-16921 A	19980805
			GB 1998-17097 A	19980807
			GB 1998-17200 A	19980808
			GB 1998-17632 A	19980814
			GB 1998-17943 A	19980819
			US 1999-325123 B1	19990603
			WO 1999-GB1779 W	19990604

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the number of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide critical clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

L9 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 29 Jan 1999
ACCESSION NUMBER: 1999:61196 CAPLUS
DOCUMENT NUMBER: 130:106058
TITLE: Bone morphogenetic protein 2-induced protein and its cDNA and their use in disease treatment and **diagnosis**
INVENTOR(S): Ahrens, Marion; Bachner, Dietmar; Hoffmann, Andrea; Lauber, Jorg; Steinert, Peter; Flohe, Leopold; Gross, Claus-Gerhard
PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung m.b.H.(GBF), Germany
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 890639	A2	19990113	EP 1998-112742	19980709
EP 890639	A3	20011010		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.: EP 1997-111602 A 19970709
AB The recombinant expression of human BMP2, BMP4 - **BMP7** in murine mesenchymal C3H10T progenitors mediates differentiation into three mesenchymal lineages with different efficiencies: the osteogenic, the chondrogenic and the adipogenic lineage. This developmental in vitro model was used to identify and to characterize cDNAs involved during the manifestation of these lineages in vivo. By subtractive cloning an as yet undescribed cDNA, 29A, has been cloned which encodes a putative secreted factor which is expressed in developing osteo- /chondrogenic tissues of vertebrae, ribs, tooth and the limb bud.

L9 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 06 Aug 1994
ACCESSION NUMBER: 1994:465548 CAPLUS
DOCUMENT NUMBER: 121:65548
TITLE: Stimulation of liver regeneration by administration of morphogenic proteins
INVENTOR(S): Kuberasampath, Thangavel; Rueger, David C.; Oppermann, Hermann; Pang, Roy H. L.; Cohen, Charles M.; Ozkaynak, Engin; Smart, John E.
PATENT ASSIGNEE(S): Creative Biomolecules, Inc., USA
SOURCE: PCT Int. Appl., 176 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 22
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9406449	A2	19940331	WO 1993-US8808	19930916
WO 9406449	A3	19940901		
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
WO 9325246	A1	19931223	WO 1993-US5446	19930608
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9345997	A1	19940104	AU 1993-45997	19930608
AU 668411	B2	19960502		
EP 646022	A1	19950405	EP 1993-916449	19930608
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07504680	T2	19950525	JP 1993-501663	19930608
JP 2908563	B2	19990621		
CA 2138270	C	20000808	CA 1993-2138270	19930608
WO 9403075	A2	19940217	WO 1993-US7190	19930729
WO 9403075	A3	19941110		
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 661933	A1	19950712	EP 1993-919858	19930729
EP 661933	B1	19980422		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

JP 07509720	T2	19951026	JP 1993-505463	19930729
AT 165213	E	19980515	AT 1993-919858	19930729
ES 2118253	T3	19980916	ES 1993-919858	19930729
EP 661987	A1	19950712	EP 1993-922700	19930916
EP 661987	B1	19980114		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08501558	T2	19960220	JP 1994-508342	19930916
AU 681356	B2	19970828	AU 1993-51623	19930916
AU 9351623	A1	19940412		
AT 162078	E	19980115	AT 1993-922700	19930916
ES 2114073	T3	19980516	ES 1993-922700	19930916
CA 2144514	C	20020326	CA 1993-2144514	19930916
US 6395883	B1	20020528	US 1995-402542	19950313
US 5849686	A	19981215	US 1995-445468	19950522
US 5834179	A	19981110	US 1995-459346	19950602
US 5652337	A	19970729	US 1995-479666	19950607
US 5652118	A	19970729	US 1995-480528	19950607
US 6071708	A	20000606	US 1997-889419	19970708
US 5854071	A	19981229	US 1997-901200	19970728
US 6153583	A	20001128	US 1998-219391	19981223
AU 9936757	A1	19990826	AU 1999-36757	19990624
AU 743061	B2	20020117		
US 2003105004	A1	20030605	US 2002-122026	20020412

PRIORITY APPLN. INFO.:

US 1992-946238	A	19920916
US 1993-29335	A	19930304
US 1993-40510	A	19930331
US 1991-667274	B2	19910311
US 1991-752964	B2	19910829
US 1991-252764		19910830
US 1991-752764	B2	19910830
US 1991-752857	B2	19910830
US 1991-752861	B2	19910830
US 1991-753059	B2	19910830
US 1992-901703	A	19920616
US 1992-922813	B2	19920731
US 1992-923780	A	19920731
US 1992-938021	B2	19920828
US 1992-938336	B2	19920828
US 1992-938337	B2	19920828
US 1992-945285	B2	19920915
US 1992-945286	B2	19920915
US 1992-946235	A	19920916
US 1992-971009	B3	19921103
US 1992-971091	B2	19921103
US 1993-27070	B2	19930304
WO 1993-US5446	A	19930608
WO 1993-US7190	W	19930729
WO 1993-US8808	W	19930916
US 1993-165541	B1	19931209
US 1995-402542	A3	19950313
US 1995-459346	A1	19950602
AU 1995-28223	A3	19950607
US 1995-479666	A3	19950607
US 1997-901200	A3	19970728

AB Methods for administering morphogenic proteins to maintain liver function or to stimulate regeneration of lost or damaged hepatic **tissue**

Searcher : Shears 571-272-2528

as a result of **disease** or phys. or chemical damage are described. Methods for appropriate gene therapy or drug delivery are described. The gene for the mouse osteogenic protein mOP-1 was found to be expressed in developing liver in the embryo. Administration of the morphogen 1-100 ng/mL to rat hepatocytes in culture stimulated DNA synthesis and cellular proliferation. Partially hepatectomized rats were treated with **OP -1** by injecting it into the liver at multiple sites along the cut line. After 12 days, the cut lobes had regenerated and reformed with no sign of the incision line; control animals injected with PBS showed no regeneration. The inhibition of inflammatory responses and fibrogenesis and scar formation by morphogen administration is demonstrated. In vitro methods for **screening** for inducers of morphogen are described.

L9 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 30 Oct 1993
ACCESSION NUMBER: 1993:574188 CAPLUS
DOCUMENT NUMBER: 119:174188
TITLE: Morphogen-induced modulation of inflammatory response
INVENTOR(S): Kuberasampath, Thangavel; Pang, Roy H. L.; Oppermann, Hermann; Rueger, David C.; Cohen, Charles M.; Ozkaynak, Engin; Smart, John E.
PATENT ASSIGNEE(S): Creative Biomolecules, Inc., USA
SOURCE: PCT Int. Appl., 167 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 22
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9304692	A1	19930318	WO 1992-US7358	19920828
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE				
AU 9225645	A1	19930405	AU 1992-25645	19920828
AU 669127	B2	19960530		
EP 601106	A1	19940615	EP 1992-919544	19920828
EP 601106	B1	20000517		
EP 601106	B2	20031105		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE				
EP 825442	A2	19980225	EP 1997-202681	19920828
EP 825442	A3	20040211		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, IE				
CA 2116562	C	19990413	CA 1992-2116562	19920828
AT 192931	E	20000615	AT 1992-919544	19920828
EP 1033574	A2	20000906	EP 2000-100232	19920828
EP 1033574	A3	20040128		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, IE				
ES 2149776	T3	20001116	ES 1992-919544	19920828
WO 9325246	A1	19931223	WO 1993-US5446	19930608
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9345997	A1	19940104	AU 1993-45997	19930608
AU 668411	B2	19960502		
EP 646022	A1	19950405	EP 1993-916449	19930608
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

JP 07504680	T2	19950525	JP 1993-501663		19930608
JP 2908563	B2	19990621			
CA 2138270	C	20000808	CA 1993-2138270		19930608
US 5656593	A	19970812	US 1993-155343		19931115
US 6211146	B1	20010403	US 1994-271556		19940707
US 5650276	A	19970722	US 1994-278729		19940720
US 6022853	A	20000208	US 1994-278730		19940720
US 6395883	B1	20020528	US 1995-402542		19950313
US 6565843	B1	20030520	US 1995-404113		19950314
US 5674844	A	19971007	US 1995-406672		19950320
US 6194376	B1	20010227	US 1995-414033		19950330
US 6288031	B1	20010911	US 1995-440894		19950515
US 5849686	A	19981215	US 1995-445468		19950522
US 6077823	A	20000620	US 1995-445467		19950522
US 5741641	A	19980421	US 1995-451953		19950526
US 5834179	A	19981110	US 1995-459346		19950602
US 5739107	A	19980414	US 1995-462623		19950605
US 5972884	A	19991026	US 1995-461397		19950605
US 6399569	B1	20020604	US 1995-461113		19950605
US 5652337	A	19970729	US 1995-479666		19950607
US 5652118	A	19970729	US 1995-480528		19950607
US 6090776	A	20000718	US 1995-480515		19950607
US 5707810	A	19980113	US 1996-643563		19960506
US 5733878	A	19980331	US 1996-643763		19960506
US 6071708	A	20000606	US 1997-889419		19970708
US 5854071	A	19981229	US 1997-901200		19970728
US 5994131	A	19991130	US 1997-912088		19970815
US 6333312	B1	20011225	US 1998-170936		19981013
US 6153583	A	20001128	US 1998-219391		19981223
AU 9936757	A1	19990826	AU 1999-36757		19990624
AU 743061	B2	20020117			
US 6531445	B1	20030311	US 1999-464206		19991215
US 2003125230	A1	20030703	US 2002-50050		20020115
US 2003105004	A1	20030605	US 2002-122026		20020412
JP 2004069670	A2	20040304	JP 2003-14941		20030123
US 2004102373	A1	20040527	US 2003-385064		20030310
JP 2004267211	A2	20040930	JP 2004-87203		20040324
PRIORITY APPLN. INFO.:			US 1991-752764	A	19910830
			US 1991-752861	A	19910830
			US 1991-753059	A	19910830
			US 1991-667274	B2	19910311
			US 1991-752964	B2	19910829
			US 1991-252764		19910830
			US 1991-752857	B2	19910830
			US 1992-901703	A	19920616
			US 1992-922813	B2	19920731
			US 1992-923780	B2	19920731
			EP 1992-921799	A3	19920828
			JP 1993-505345	A3	19920828
			US 1992-938021	B1	19920828
			US 1992-938336	B2	19920828
			US 1992-938337	B2	19920828
			WO 1992-US7358	A	19920828
			US 1992-945285	B1	19920915
			US 1992-945286	B1	19920915
			US 1992-945292	B1	19920915

Searcher : Shears 571-272-2528

US 1992-946235	B1	19920916
US 1992-946238	B1	19920916
US 1992-971009	B3	19921103
US 1992-971091	B2	19921103
US 1993-27070	B2	19930304
US 1993-29335	B2	19930304
US 1993-40510	B1	19930331
WO 1993-US5446	A	19930608
US 1993-89424	B1	19930707
US 1993-91395	B1	19930713
US 1993-115914	B1	19930901
US 1993-152901	B1	19931115
US 1993-155343	A1	19931115
US 1993-165511	B1	19931209
US 1993-165541	B1	19931209
US 1993-174605	B1	19931228
US 1994-278729	A1	19940720
US 1995-396684	A3	19950301
US 1995-402542	A3	19950313
US 1995-414033	A1	19950330
US 1995-432883	B1	19950502
US 1995-451953	A3	19950526
US 1995-459346	A1	19950602
US 1995-461113	A1	19950605
AU 1995-28223	A3	19950607
US 1995-479666	A3	19950607
US 1997-901200	A3	19970728
US 1999-464206	A1	19991215

AB Methods and compns. are provided for alleviating tissue destructive effects associated with the inflammatory response to tissue injury in a mammal. The methods and compns. include administering a therapeutically effective concentration of a morphogen (morphogenic protein) or morphogen-stimulating agent sufficient to alleviate immune cell-mediated tissue destruction. Morphogen **OP-1** offered significant cardiac protection when administered after ischemia and before reperfusion in a rat model. Morphogen inhibition of epithelial cell proliferation, morphogen inhibition of localized edema, morphogen treatment of exptl. allergic encephalomyelitis, etc., are also described.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 15:36:37 ON 17 DEC 2004)

L10 52 S L9
L11 41 DUP REM L10 (11 DUPLICATES REMOVED)

L11 ANSWER 1 OF 41 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:728587 SCISEARCH
THE GENUINE ARTICLE: 844UG
TITLE: Differential gene expression and regulation of the bone morphogenetic protein antagonists follistatin and gremlin in normal and osteoarthritic
AUTHOR: Tardif G; Hum D; Pelletier J P; Boileau C; Ranger P; Martel-Pelletier J (Reprint)
CORPORATE SOURCE: CHU Montreal, Hop Notre Dame de Bon Secours, Osteoarthritis Res Unit, 1560 Sherbrooke St E, Montreal, PQ H2L 4M1, Canada (Reprint); CHU Montreal, Hop Notre Dame

de Bon Secours, Osteoarthritis Res Unit, Montreal, PQ H2L 4M1, Canada; Hop Sacre Coeur, Montreal, PQ H4J 1C5, Canada
COUNTRY OF AUTHOR: Canada
SOURCE: ARTHRITIS AND RHEUMATISM, (AUG 2004) Vol. 50, No. 8, pp. 2521-2530.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA.
ISSN: 0004-3591.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 49

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective. To compare gene expression in normal and osteoarthritic (OA) human chondrocytes using microarray technology. Of the novel genes identified, we selected follistatin, a bone morphogenetic protein (BMP) antagonist, and investigated its expression/regulation as well as that of 3 other antagonists, gremlin, chordin, and noggin, in normal and OA chondrocytes and synovial fibroblasts.

Methods. Basal and induced gene expression were **determined** using real-time polymerase chain reaction. Gene regulation was monitored following treatment with inflammatory, antiinflammatory, growth, and developmental factors. Follistatin protein production was **measured** using a specific enzyme-linked immunosorbent assay, and localization of follistatin and gremlin in cartilage was **determined** by immunohistochemical analysis.

Results. All BMP antagonists except noggin were expressed in chondrocytes and synovial fibroblasts. Follistatin and gremlin were significantly up-regulated in OA chondrocytes but not in OA synovial fibroblasts. Chordin was weakly expressed in normal and OA cells. Production of follistatin protein paralleled the gene expression pattern. Follistatin and gremlin were expressed preferentially by the chondrocytes at the superficial layers of cartilage. Tumor necrosis factor a and interferon-gamma significantly stimulated follistatin expression but down-regulated expression of gremlin. Interleukin-1beta (IL-1beta) had no effect on follistatin but reduced gremlin expression. Conversely, BMP-2 and BMP-4 significantly stimulated expression of gremlin but down-regulated that of follistatin. IL-13, dexamethasone, transforming growth factor beta1, basic fibroblast growth factor, platelet-derived growth factor type BB, and endothelial cell growth factor down-regulated the expression of both antagonists.

Conclusion. This study is the first to show the possible involvement of follistatin and gremlin in OA pathophysiology. The increased activin/BMP-binding activities of these antagonists could affect **tissue** remodeling. The data suggest that follistatin and gremlin might appear at different stages during the OA process, making them interesting targets for the treatment of this **disease**.

L11 ANSWER 2 OF 41 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:430944 SCISEARCH
THE GENUINE ARTICLE: 817DB
TITLE: Connective tissue growth factor is increased in plasma of type 1 diabetic patients with nephropathy
AUTHOR: Roestenberg P; van Nieuwenhoven F A; Wieten L; Boer P; Diekman T; Tiller A M; Wiersinga W M; Oliver N; Usinger W; Weitz S; Schlingemann R O; Goldschmeding R (Reprint)

CORPORATE SOURCE: Univ Utrecht, Ctr Med, Dept Pathol, H04 312, Heidelberglaan 100, NL-3584 CX Utrecht, Netherlands (Reprint); Univ Utrecht, Ctr Med, Dept Pathol, NL-3584 CX Utrecht, Netherlands; Univ Utrecht, Ctr Med, Dept Hypertens & Nephrol, NL-3584 CX Utrecht, Netherlands; Acad Med Ctr, Dept Endocrinol & Metab, Amsterdam, Netherlands; Acad Med Ctr, Dept Ophthalmol, Amsterdam, Netherlands; FibroGen, San Francisco, CA USA
COUNTRY OF AUTHOR: Netherlands; USA
SOURCE: DIABETES CARE, (MAY 2004) Vol. 27, No. 5, pp. 1164-1170. Publisher: AMER DIABETES ASSOC, 1701 N BEAUREGARD ST, ALEXANDRIA, VA 22311-1717 USA. ISSN: 0149-5992.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 31

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB OBJECTIVE - Connective **tissue** growth factor (CTGF) is strongly upregulated in Fibrotic **disorders** and has been hypothesized to play a role in the development and progression of diabetes complications. The aim of the present study was to investigate the possible association of plasma CTGF levels in type I diabetic patients with markers relevant to development of diabetes complications.

RESEARCH DESIGN AND METHODS - Plasma CTGF levels (full-length and NH2-terminal fragments) were **determined** in 62 well-characterized patients with type 1 diabetes and in 21 healthy control subjects. Correlations of these plasma CTGF levels with markers of glycemic control, platelet activation, endothelial activation, nephropathy, and retinopathy were investigated.

RESULTS - Elevated plasma NH2-terminal fragment of CTGF (CTGF-N) levels were **detected** in a subpopulation of type I diabetic patients and were associated with diabetic nephropathy. Stepwise regression analysis revealed contribution of atbuminuria, creatinine clearance, and duration of diabetes as predictors of plasma CTGF-N level. Elevation of plasma CTGF-N levels in patients with retinopathy was probably clue to renal comorbidity.

CONCLUSIONS - Plasma CTGF-N levels are elevated in type 1 diabetic patients with nephropathy and appear to be correlated with proteinuria and creatinine clearance. Further studies will be needed to **determine** the relevance of plasma CTGF as a clinical marker and/or pathogenic factor in diabetic nephropathy.

L11 ANSWER 3 OF 41 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2004371935 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15277215
TITLE: Differential gene expression in ovarian carcinoma: identification of potential biomarkers.
AUTHOR: Hibbs Kathleen; Skubitz Keith M; Pambuccian Stefan E; Casey Rachael C; Burleson Kathryn M; Oegema Theodore R Jr; Thiele Jeannine J; Grindle Suzanne M; Bliss Robin L; Skubitz Amy P N
CORPORATE SOURCE: Department of Laboratory Medicine and Pathology, University of Minnesota, MMC 609, 420 Delaware St. S.E., Minneapolis, MN 55455, USA.
CONTRACT NUMBER: CA0913825 (NCI)
SOURCE: American journal of pathology, (2004 Aug) 165 (2) 397-414.

Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 20040728
Last Updated on STN: 20040825
Entered Medline: 20040824

AB Ovarian cancer remains the fifth leading cause of cancer death for women in the United States. In this study, the gene expression of 20 ovarian carcinomas, 17 ovarian carcinomas metastatic to the omentum, and 50 normal ovaries was **determined** by Gene Logic Inc. using Affymetrix GeneChip HU_95 arrays containing approximately 12,000 known genes. Differences in gene expression were **quantified** as fold changes in gene expression in ovarian carcinomas compared to normal ovaries and ovarian carcinoma metastases. Genes up-regulated in ovarian carcinoma **tissue** samples compared to more than 300 other normal and **diseased tissue** samples were identified. Seven genes were selected for further **screening** by immunohistochemistry to **determine** the presence and localization of the proteins. These seven genes were: the beta8 integrin subunit, **bone morphogenetic protein-7**, claudin-4, collagen type IX alpha2, cellular retinoic acid binding protein-1, forkhead box J1, and S100 calcium-binding protein A1. Statistical analyses showed that the beta8 integrin subunit, claudin-4, and S100A1 provided the best distinction between ovarian carcinoma and normal ovary tissues, and may serve as the best candidate tumor markers among the seven genes studied. These results suggest that further exploration into other up-regulated genes may identify novel **diagnostic**, therapeutic, and/or prognostic biomarkers in ovarian carcinoma.

L11 ANSWER 4 OF 41 EMBASE
on STN

ACCESSION NUMBER: 2004279448 EMBASE
TITLE: Differential expression of osteogenic factors associated with osteoinductivity of human osteosarcoma cell lines.
AUTHOR: Yu Y.; Harris R.I.; Yang J.-L.; Anderson H.C.; Walsh W.R.
CORPORATE SOURCE: Y. Yu, Orthopaedic Research Laboratory, University of New South Wales, Prince of Wales Hospital, Sydney, NSW 2031, Australia. y.yu@unsw.edu.au
SOURCE: Journal of Biomedical Materials Research - Part A, (1 Jul 2004) 70/1 (122-128).
Refs: 31
ISSN: 0021-9304 CODEN: JBMRCH
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
033 Orthopedic Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Differential expression of multiple osteogenic factors may be responsible for the different osteoinductivity of osteosarcoma cell lines. We compared in vivo osteoinductivity of human osteosarcoma cell lines (Saos-2 vs. U-2 OS) in nude mice, and their in vitro expression of various osteogenic

factors of protein level by **quantitative** immunocytochemistry and mRNA level by RT-PCR and/or in situ hybridization. Saos-2 cells, but not U-2 OS, were osteoinductive in vivo. Significantly higher expression (independent t-test, all $p < 0.005$) of osteogenic factors were observed in Saos-2 cells compared with U-2 OS, which included bone morphogenetic proteins (particularly BMPs-2, 3, 4, and 7), transforming growth factor-beta (TGF-β), BMP receptor (BMPR)-1A, receptor-regulated Smads (R-Smads), Smads 1, 2, and 5, and common-mediator Smad (Co-Smad), Smad 4. In contrast, U-2 OS cells expressed higher levels of inhibitory Smad 6 (I-Smad) protein than Saos-2 cells ($p < 0.001$). These results suggest that a combination of osteogenic factors (BMPs, TGF-β, BMPRs, and R/Co-Smads) against I-Smad may play important roles in the Saos-2 cell osteoinductivity. This may have a clinical implication in selecting key osteogenic factors for combined therapy for bone defect **diseases** . The characterized cell lines can be used as positive and negative controls for the assessments of both in vitro and in vivo bone formation capabilities of designed **tissues** or biomaterials. .COPYRGT. 2004 Wiley Periodicals, Inc.

L11 ANSWER 5 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-416693 [39] WPIDS
DOC. NO. NON-CPI: N2003-332157
DOC. NO. CPI: C2003-110268
TITLE: **Quantification** of osteoinductive potential of implant materials for implantation to patient, by **quantifying** concentration of osteogenic factor present in implant releasate, in vitro and without implanting material in vivo.
DERWENT CLASS: B04 D16 D22 S03
INVENTOR(S): JAW, R; WIRONEN, J F
PATENT ASSIGNEE(S): (JAWR-I) JAW R; (WIRO-I) WIRONEN J F; (REGE-N) REGENERATION TECHNOLOGIES INC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003008328	A1	20030109	(200339)*		30
WO 2003004990	A2	20030116	(200339)	EN	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW					
AU 2002318482	A1	20030121	(200452)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003008328	A1	US 2001-897728	20010703
WO 2003004990	A2	WO 2002-US21026	20020703
AU 2002318482	A1	AU 2002-318482	20020703

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002318482	A1 Based on	WO 2003004990

PRIORITY APPLN. INFO: US 2001-897728 20010703
AN 2003-416693 [39] WPIDS
AB US2003008328 A UPAB: 20030619
NOVELTY - **Quantifying** an osteoinductive potential of implant materials by releasing osteogenic factors from a representative sampling of materials, **quantifying** the concentration of osteogenic factor present in an implant releasate in vitro without implanting materials in vivo or use of complex biological living material, and **determining** osteogenic potential for the representative sampling, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) accelerating wound healing by producing a composition comprising at least two growth factors, and administering the composition to a patient;

(2) **diagnosis** and treatment of bone or soft-tissue cancer in a human or non-human patient by:

(a) harvesting bone or soft-tissue from a donor;

(b) isolating and purifying osteogenic material; and

(c) comparing the **quantity** and type of growth factors present to that of found in healthy bone or other tissues; and

(3) assessing developmental bone or **tissue disorders** by:

(a) performing **diagnosis** and treatment of bone or soft-tissue cancer in patient; and

(b) identifying osteogenic factors present in elevated or decreased concentrations relative to the baseline value.

ACTIVITY - Vulnerary.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - The method is for **quantifying** the osteoinductive potential of a collection of like implant material for implantation to human or non-human recipients.

ADVANTAGE - The inventive method permits direct **measurement** of the osteogenic capacity of an implant, thus allowing greater predictability of the degree to which new bone will grow in a given area. It eliminates the need to practice the traditional technique of implanting material into a test animal to assess bone growth associated with implant. It is extremely reproducible, rapid, and accurate for predicting whether an implant composition or material will induce bone growth without the need for in vivo assay.

Dwg.0/19

L11 ANSWER 6 OF 41 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 2

ACCESSION NUMBER: 2003348953 EMBASE
TITLE: Alterations in endogenous **osteogenic protein-1** with degeneration of human articular cartilage.
AUTHOR: Merrihew C.; Kumar B.; Heretis K.; Rueger D.C.; Kuettner K.E.; Chubinskaya S.
CORPORATE SOURCE: S. Chubinskaya, Department of Biochemistry, Rush Medical College, Rush-Presbyt.-St. Luke's Med. Center, 1653 W.

Congress Parkway, Chicago, IL 60612, United States.
schubins@rush.edu
SOURCE: Journal of Orthopaedic Research, (2003) 21/5 (899-907).
Refs: 38
ISSN: 0736-0266 CODEN: JOREDR
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
031 Arthritis and Rheumatism
033 Orthopedic Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A synchronized balance between synthesis and breakdown of extracellular matrix (ECM) molecules in normal articular cartilage is disturbed in osteoarthritis (OA). The focus of our study is the anabolic factor, **osteogenic protein-1** (**OP-1**) that is expressed in articular cartilage and is able to induce the synthesis of ECM components. The major aim was to investigate both qualitatively and **quantitatively** endogenous **OP-1** in normal, degenerative, and OA cartilage. Normal and degenerative cartilage was obtained at autopsies from femoral condyles of human organ donors with no documented history of joint **disease**; OA cartilage was obtained from patients undergoing joint arthroplasty. Appearance of donor cartilage was evaluated by Collins scale, where normal cartilage is assigned grades 0-1, and degenerated cartilage is assigned grades 2-4. **OP-1** mRNA expression was assessed by RT-PCR; **OP-1** protein (pro- and active forms) was qualitatively analyzed by Western blotting and **quantified** by **OP-1** ELISA. The highest levels of **OP-1** expression (mRNA and protein) were **detected** in normal cartilage of grade 0. The concentration of **OP-1** protein was about 50 ng per gram cartilage dry weight. With the progression of cartilage degeneration (increased Collins grades and OA) **OP-1** protein was down-regulated up to 9-fold. These changes affected primarily the active form of **OP-1**. **OP-1** message also declined in cartilages with the increase of degenerative changes. In conclusion, an overall decrease in endogenous **OP-1** in degenerated and OA **tissue** suggests that **OP-1** could be one of the factors responsible for normal homeostasis and matrix integrity in cartilage. .COPYRGT. 2003 Orthopaedic Research Society. Published by Elsevier Ltd. All rights reserved.

L11 ANSWER 7 OF 41 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:808645 SCISEARCH
THE GENUINE ARTICLE: 720QP
TITLE: SOX9 expression does not correlate with type II collagen expression in adult articular chondrocytes
AUTHOR: Aigner T (Reprint); Gebhard P M; Schmid E; Bau B; Harley V; Poschl E
CORPORATE SOURCE: Univ Erlangen Nurnberg, Dept Pathol, Krankenhausstr 8-10, D-91504 Erlangen, Germany (Reprint); Univ Erlangen Nurnberg, Dept Pathol, D-91504 Erlangen, Germany; Prince Henrys Inst Med Res, Melbourne, Vic, Australia; Univ Erlangen Nurnberg, Dept Expt Med 1, D-91504 Erlangen,

Germany
COUNTRY OF AUTHOR: Germany; Australia
SOURCE: MATRIX BIOLOGY, (JUN 2003) Vol. 22, No. 4, pp. 363-372.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0945-053X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Anabolic activity is a crucial activity of articular chondrocytes and its failure is one major reason of osteoarthritic cartilage degeneration. The intracellular factors responsible for the increase or decrease of anabolic activity of articular chondrocytes remain largely unknown. A recent candidate, the transcription factor SOX9, has elicited much interest as it is suggested to be a central factor in chondrocytic differentiation during development, including collagen type II (COL2A1) expression, the major anabolic gene product of chondrocytes. Here we show that normal adult human articular chondrocytes in vivo contain high SOX9 mRNA levels, which are decreased in osteoarthritic cartilage. Surprisingly, no positive correlation between SOX9 and COL2A1 expression was observed-to the contrary, the expression of COL2A1 was significantly increased in the **diseased** cells. Immunolocalization confirmed the presence of SOX9 protein in normal and osteoarthritic chondrocytes without showing significant differences in both SOX9 **quantity** and subcellular localization in osteoarthritic compared to normal cartilage **tissue**. Interestingly, laser scanning confocal microscopy showed that the subcellular distribution of SOX9 in adult chondrocytes was not restricted to the nucleus as observed in fetal chondrocytes, but was also **detected** within the cytoplasm, with no differences in subcellular SOX9 distribution between normal and OA cartilage. This is consistent with the lack of positive correlation between SOX9 and COL2A1 expression in adult articular chondrocytes. Also, no positive correlation between SOX9 and COL2A1 expression was observed in vitro after challenge of chondrocytes with Il-1beta, which is a strong (negative) regulator of COL2A1 expression, or with IGF-I, which stimulates COL2A1 expression. These results suggest that SOX9 is not the key regulator of COL2A1 promoter activity in human adult articular chondrocytes. However, SOX9 might still be involved in maintaining the chondrocytic phenotype in normal and osteoarthritic cartilage. (C) 2003 Elsevier Science B.V/Intemational Society of Matrix Biology All rights reserved.

ACCESSION NUMBER: 2003319578 EMBASE
TITLE: Structural basis of BMP signaling inhibition by Noggin, a novel twelve-membered cystine knot protein.
AUTHOR: Groppe J.; Greenwald J.; Wiater E.; Rodriguez-Leon J.; Economides A.N.; Kwiatkowski W.; Baban K.; Affolter M.; Vale W.W.; Izpisua Belmonte J.C.; Choe S.
CORPORATE SOURCE: Dr. J. Groppe, Structural Biology Laboratory, Salk Institute, 10010 North Torrey Pines Road, San Diago, CA 92037, United States. groppe@salk.edu
SOURCE: Journal of Bone and Joint Surgery - Series A, (1 Aug 2003) 85/SUPPL. 3 (52-58).

Refs: 30
ISSN: 0021-9355 CODEN: JBJSA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: The activity of bone morphogenetic proteins (BMPs) is regulated extracellularly by several families of secreted, negatively-acting factors. These BMP antagonists participate in the control of a diverse range of embryonic processes, such as establishment of the dorsal-ventral axis, neural induction, and formation of joints in the developing skeletal system. The ongoing process of neurogenesis in the adult brain also requires inhibition of BMP ligand activity. To date, the three-dimensional structures of these antagonists as well as the nature of their interaction with ligand have remained unknown. Toward that end, we have **determined** the crystal structure of the antagonist Noggin bound to **BMP-7**. Methods: The complex of the two homodimeric proteins was preformed, isolated by size exclusion chromatography, and crystallized at neutral pH. To probe the molecular interface of the complex and to **quantitate** the activity of a human mutant form, variant Noggin proteins were produced and their binding affinities were **measured** in vitro. The correlation between binding affinity and biological activity was examined with Noggin-soaked beads implanted in the developing chick limb bud. Results and Conclusions: The structure of the complex reveals that Noggin inhibits BMP signaling by blocking the binding sites of both types of receptors (Type I and Type II), mimicking their modes of binding. The affinity of Noggin variants for **BMP-7** correlated well with the inhibition of BMP-induced chondrogenesis in the chick limb bud, confirming that Noggin acts by sequestering the ligand in an inactive state. Interestingly, the scaffold of Noggin was found to contain a cystine knot topology and protein fold similar to that of BMPs, indicating that ligand and antagonist may have evolved from a common ancestral gene. Clinical Relevance: Mutations in the human Noggin locus (NOG) are associated with three similar yet distinct skeletal dysplasias: proximal symphalangism (SYM1), multiple synostoses syndrome (SYNS1), and tarsal-carpal coalition syndrome (TCC). The crystal structure of the Noggin:**BMP-7** complex provides a structural context for interpreting the effects of missense mutations with respect to Noggin protein folding, stability, or activity. The structure also provides the basis for engineering variants of Noggin that may have therapeutic applications in the treatment of fibrodysplasia ossificans progressiva (FOP), a rare genetic **disorder** of connective **tissue** resulting from lymphocytic misexpression of BMPs.

L11 ANSWER 9 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-167376 [16] WPIDS
DOC. NO. NON-CPI: N2003-132261
DOC. NO. CPI: C2003-043505
TITLE: New pharmaceutical composition or scaffold useful for aiding in regeneration of tissues such as bone and cartilage, comprises bone morphogenetic protein binding protein.
DERWENT CLASS: B04 D16 P32

INVENTOR(S): HARRISON, A J; MUSTILL, W J; SCULLY, A J; THOMSON, B M
PATENT ASSIGNEE(S): (SMIN) SMITH & NEPHEW PLC; (HARR-I) HARRISON A J; (MUST-I) MUSTILL W J; (SCUL-I) SCULLY A J; (THOM-I) THOMSON B M
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002100426	A1	20021219	(200316)*	EN	131
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
NO 2003005453	A	20040209	(200419)		
EP 1399177	A1	20040324	(200421)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
AU 2002302768	A1	20021223	(200452)		
US 2004176287	A1	20040909	(200459)		
JP 2004536818	W	20041209	(200481)		196

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002100426	A1	WO 2002-GB2427	20020610
NO 2003005453	A	WO 2002-GB2427	20020610
		NO 2003-5453	20031208
EP 1399177	A1	EP 2002-730447	20020610
		WO 2002-GB2427	20020610
AU 2002302768	A1	AU 2002-302768	20020610
US 2004176287	A1	WO 2002-GB2427	20020610
		US 2004-479747	20040504
JP 2004536818	W	WO 2002-GB2427	20020610
		JP 2003-503246	20020610

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1399177	A1	Based on	WO 2002100426
AU 2002302768	A1	Based on	WO 2002100426
JP 2004536818	W	Based on	WO 2002100426

PRIORITY APPLN. INFO: GB 2002-437 20020110; GB 2001-13606 20010608
AN 2003-167376 [16] WPIDS
AB WO2002100426 A UPAB: 20030307
NOVELTY - A pharmaceutical composition (I) or a scaffold (II) for promoting tissue generation, comprises a bone morphogenetic protein (BMP) binding protein (III).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the

following:

(1) use of (III) in the manufacture of a medicament for the treatment of a **disease** or clinical conditions that may be alleviated by the production of **tissue** regeneration e.g. cartilage and/or bone **tissue** regeneration;

(2) a device for promoting tissue regeneration, comprising (I); and

(3) manufacturing (II), by coating a scaffold with (III).

ACTIVITY - Osteopathic; Cytostatic; Antirheumatic; Antiarthritic.

MECHANISM OF ACTION - Tissue (bone and cartilage) regeneration and growth inducer (claimed). Effects of follistatin and BMP-2,6 and 7 on C2C12 cells were **determined** as follows: Four conditions were initially set up in wells of a 96 well plate:

(i) 50 micro l of follistatin;

(ii) 50 micro l of follistatin;

(iii) tissue culture plastic (TCP); and

(iv) TCP.

The above solutions were added to the wells of a 96 well tissue culture plate and left to incubate overnight at 4 deg. C. Following incubation, the protein solutions were removed and the wells washed three times with phosphate buffered saline (PBS). To the well in conditions (ii) and (iii) either 125.5 micro l/well of BMP-2 (1 micro g ml-1) or 142.5 micro l/well of BMP-6 (1 micro g ml-1) or 121.5 micro l/well of **BMP-7** (1 micro g ml-1) was added. One hundred micro l/well of serum free Dulbecco's Modified Eagle Medium (SFDMEM) was added to the wells in conditions (i) and (iv). The solutions were incubated for 1 hour at 37 deg. C/5 % CO2. One hundred l of C2C12 cells (European Collection of Cell Cultures (ECACC) lot 91031101) were cultured in the wells at a cell density of 3.4 multiply 104 cells ml-1 and incubated at 37 deg. C/5 % CO2 in a humidified atmosphere for approximately 4 days. After 4 days, the cells were lyzed using the freeze thaw method, alkaline phosphatase activity was assessed using the pNitrophenyl-phosphate alkaline phosphatase assay (pNPP) assay and normalized to DNA levels using the PicoGreen (RTM) assay outlined in the general methods section. Results showed an increase in alkaline phosphatase expressed by cultures grown in conditions of follistatin and BMP, compared to those cultures grown in BMP alone, indicating that these cells have been stimulated to differentiate further along an osteoblastic lineage. The result therefore suggested that cells that responded to follistatin and BMP resulting in a higher level of osteogenic tissue regeneration.

USE - (I) is useful to aid in **tissue** regeneration, where the **tissue** is bone or cartilage. (III) is used in the manufacture of a medicament for the treatment of a **disease** or clinical conditions that may be alleviated by the production of **tissue** regeneration e.g. cartilage and/or bone **tissue** regeneration, and for manufacturing (II) (claimed). (III) is useful for treating osteoporosis (including osteoporosis of disuse, Schuller's **disease**, post-menopausal osteoporosis, post-traumatic osteoporosis and senile osteoporosis), Paget's **disease**, undesired bone resorption featured in cancer and renal **disease**, and rheumatoid arthritis. (III) is also useful for treating bone and cartilage repair, and for inducing bone and cartilage growth.

ADVANTAGE - (III) is suitable for treating bone and cartilage repair and for inducing bone and cartilage growth without a large concentration of (III) being needed. Using large concentrations of growth factors has been a problem as this suffers from the disadvantage that a large concentration of the growth factor can cause a shift in biological

equilibrium possibly making the growth factor less potent.
Dwg.0/2

L11 ANSWER 10 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-239101 [23] WPIDS
DOC. NO. CPI: C2003-061206
TITLE: Novel compound useful for treating cancer, tumors and inflammatory diseases, cleavable by CD10, and has therapeutic agent capable of entering target cell, oligopeptide, stabilizing group and linker group.
DERWENT CLASS: A96 B04 D16
INVENTOR(S): BEBBINGTON, C R; CARDARELLI, P M; GANGWAR, S; NIEDER, M H; PAN, C; PICKFORD, L B
PATENT ASSIGNEE(S): (MEDA-N) MEDAREX INC; (BEBB-I) BEBBINGTON C R; (CARD-I) CARDARELLI P M; (GANG-I) GANGWAR S; (NIED-I) NIEDER M H; (PANC-I) PAN C; (PICK-I) PICKFORD L B
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002100353	A2	20021219	(200323)*	EN	167
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
EP 1404356	A2	20040407	(200425)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2004087497	A1	20040506	(200430)		
AU 2002316539	A1	20021223	(200452)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002100353	A2	WO 2002-US21135	20020610
EP 1404356	A2	EP 2002-746852	20020611
		WO 2002-US21135	20020611
US 2004087497	A1 Provisional	US 2001-297596P	20010611
		US 2002-167627	20020611
AU 2002316539	A1	AU 2002-316539	20020610

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1404356	A2 Based on	WO 2002100353
AU 2002316539	A1 Based on	WO 2002100353

PRIORITY APPLN. INFO: US 2001-297596P 20010611; US 2002-167627 20020611
AN 2003-239101 [23] WPIDS

Searcher : Shears 571-272-2528

AB WO2002100353 A UPAB: 20030407
NOVELTY - A compound (I) comprising therapeutic agent (TA) capable of entering target cell, oligopeptide (OP), stabilizing group (SG) and optionally, linker group (LG), and cleavable by CD10, is new.

DETAILED DESCRIPTION - OP is directly linked to SG at first attachment site of OP and OP is directly linked to TA or indirectly linked through LG to TA at second attachment site of OP, and SG hinders cleavage of (I) by enzymes present in blood.

(I) comprises TA capable of entering a target cell, OP of the formula (AA)n-AA(P2)-AA(P1)-AA(P1')-(AA)m, where n and m are integers, AA(P2), AA(P1) and AA(P1') represents any amino acid, and each AA independently represents an amino acid, SG, and optionally, LG, where (I) is cleavable by CD10, OP is directly linked to SG at a first attachment site of OP and OP is directly linked to TA or indirectly linked through LG to TA at a second attachment site of OP, SG hinders cleavage of (I) by enzymes present in whole blood, if OP is Leu-Ala-Leu, then SG is not succinyl or beta Ala or TA is not one of doxorubicin and daunorubicin, if OP is beta Ala-Leu-Ala-Leu, then SG is not succinyl or TA is not one of doxorubicin and daunorubicin, if OP is beta Ala-Leu-Ala-Leu, then SG is not glutaryl or TA is not doxorubicin, and (I) is not chosen from Succ-Ala-Leu-Ala-Leu-Dnr, pGlu-Ala-Leu-Ala-Leu-Dox, D-Ala-Leu-Ala-Leu-Dnr, D-Leu-Ala-Leu-Ala-Leu-Dnr, D-Leu-D-Ala-Leu-Ala-Leu-Dnr, Acetyl-His-Ser-Ser-Lys-Leu-Gln-Dox, Morpholinocarbonyl-His-Ser-Ser-Lys-Leu-Gln-Leu-Dox, N-(2-hydroxypropyl)methacrylamide-Gly-Phe-Leu-Gly-Dox, N-glutaryl-(4-hydroxyprolyl)-Ala-Ser-Cyclohexylglycine- Gln-Ser-Leu-Dox, N-Cbz-Gly-Phe-Ala-Leu-Dox and N-Cbz-Gly-Phe-Ala-Leu-PABC-Dox.

INDEPENDENT CLAIMS are also included for:

(1) a conjugate (II) comprising OP which is cleavable by CD10 or thermolysin-like enzyme;

(2) a pharmaceutical composition (III) comprising (I) and a carrier;

(3) production (M) of (I);

(4) a prodrug produced by (M);

(5) **screening** to identify OP useful for designing a prodrug, by providing (I), and testing if OP is cleavable by CD10, where cleavability by CD10 is indicative of OP as a candidate for designing a prodrug; and

(6) an article of manufacture for **diagnosis** or assay comprising (I) which has a marker, OP, SG, and optionally LG not cleavable by CD10, and a reagent useful in the **detection** of the marker.

ACTIVITY - Cytostatic; Antiinflammatory; Anti-tumor.

The effect of Suc- beta Ala-Ile-Ala-Leu-Dox therapeutic agent on the survival of mice and on growth of the tumors in a mouse xenograft model was evaluated. Groups of ten nude mice, were subcutaneously implanted with chunks of doxorubicin-resistant colorectal carcinoma LS174t, and were allowed to grow to approximately 50 mg. They were treated intravenously with 0, 53 or 68 mg/kg of Suc- beta Ala-Ile-Ala-Leu-Dox (equivalent to 0, 30 or 38 mg/kg doxorubicin) at five day intervals for a total of five identical doses. Tumors and body weights were **measured** twice weekly for up to 60 days. Both doses were efficacious in reducing the growth of tumors compared with vehicle control animals. There were 4 and 2 long-term survivors in the low and high dose groups, respectively, compared with 0 in the vehicle control group. The Mean Day of Survival (MDS) in animals whose tumors reached 1.5 g prior to day 60 was significantly better in the low (29.7 days) and high (23.4 day) dose groups than in the vehicle control group (18.2 days). Thus, Suc- beta Ala-Ile-Ala-Leu-Dox was efficacious in this aggressive human tumor model,

in which doxorubicin alone at its tolerated dose (3 mg/kg), under this dosing regimen, was ineffective.

MECHANISM OF ACTION - Inhibitor of tumor growth.

USE - (I) is useful for manufacturing a medicament for treating a **disorder** having CD10-associated target cells, such as cancer (e.g. prostate cancer, B-cell lymphoblastic leukemia, T-cell lymphoblastic leukemia, lymphoma, including B-cell lymphoma and non-Hodgkins' lymphoma, follicular lymphoma, Burkitt lymphoma, melanoma, ocular melanoma, cutaneous melanoma, colon adenocarcinomas, hepatocellular carcinomas, renal cell carcinoma, ovarian carcinoma, prostate adenocarcinoma, liver carcinoma, transitional cell carcinoma, pancreatic adenocarcinoma, lung carcinoma, breast carcinoma and colon carcinoma), neoplastic **diseases**, tumors, inflammatory **diseases**, and infectious **diseases**. The method involves **detecting** CD10 associated with a target cell, and administering (I) to the patient. The **detecting** step involves obtaining a sample of **tissue**, combining the sample with a CD10-specific antibody, and **determining** binding of the CD-10 specific antibody to the sample. (I) is also useful for decreasing toxicity of TA which is intended for administration to a patient, by covalently forming a prodrug by linking OP cleavable by CD10 to SG at a first attachment site of OP and directly or indirectly linking TA at a second attachment site of OP, so that the prodrug is cleavable by CD10. The prodrug allows for administration of an increased dosage of TA in prodrug form to the patient relative to the dosage of TA in unconjugated form (all claimed). (I) is useful for **diagnosing** CD10 positive tumors.

ADVANTAGE - (I) has high specificity of action, reduced toxicity, improved stability in the serum and blood, improved therapeutic index, favorable pharmacokinetics, and does not move into target cells, or moves only minimally until activated by CD10.

DESCRIPTION OF DRAWING(S) - The figure is a schematic diagram showing cleavage of a prodrug in the extracellular vicinity of the target cell and within the target cell.

Dwg.2/35

L11 ANSWER 11 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-698683 [75] WPIDS
DOC. NO. NON-CPI: N2002-550921
DOC. NO. CPI: C2002-197890
TITLE: **Determining** the presence of e.g. an inflammatory **disease** or autoimmune **disease**, useful for **determining** predisposition to such **diseases**, comprises **determining** the level of **osteogenic protein-1** protein or mRNA in a joint **tissue** sample.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): CHUBINSKAYA, S; KUETTNER, K E; RUEGER, D C
PATENT ASSIGNEE(S): (CHUB-I) CHUBINSKAYA S; (KUET-I) KUETTNER K E; (RUEG-I) RUEGER D C; (STYC) STRYKER CORP
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002068962	A2	20020906	(200275)*	EN	54

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

US 2002192679 A1 20021219 (200303)
EP 1390757 A2 20040225 (200415) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
AU 2002240493 A1 20020912 (200433)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002068962	A2	WO 2002-US5551	20020220
US 2002192679	A1 Provisional	US 2001-270528P	20010221
	Provisional	US 2001-348111P	20011109
		US 2002-81163	20020220
EP 1390757	A2	EP 2002-706405	20020220
		WO 2002-US5551	20020220
AU 2002240493	A1	AU 2002-240493	20020220

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1390757	A2 Based on	WO 2002068962
AU 2002240493	A1 Based on	WO 2002068962

PRIORITY APPLN. INFO: US 2001-348111P 20011109; US 2001-270528P 20010221; US 2002-81163 20020220

AN 2002-698683 [75] WPIDS

AB WO 200268962 A UPAB: 20021120

NOVELTY - **Determining** (M1) the presence of an inflammatory **disease**, an age-related **tissue disorder**, a **disorder** characterized by accelerated or abnormal **tissue** aging, an autoimmune **disease**, or a predisposition to a **disease** resulting in cartilage degradation or degeneration, comprising **determining** an amount of **osteogenic protein-1** (**OP-1**) protein or mRNA in a joint **tissue** sample, is new.

DETAILED DESCRIPTION - **Determining** (M1) the presence of an inflammatory **disease**, an age-related **tissue disorder**, a **disorder** characterized by accelerated or abnormal **tissue** aging, an autoimmune **disease**, or a predisposition to a **disease** resulting in cartilage degradation or degeneration, comprises:

(a) **determining** an amount of **osteogenic protein-1** (**OP-1**) protein or mRNA in a joint tissue sample; and

(b) comparing the amount of **OP-1** protein with a pre-**determined** standard, where a difference in the amount of

OP-1 protein presence in the sample and the pre-**determined** standard indicates the presence of the disease or disorder.

INDEPENDENT CLAIMS are also included for:

(1) **determining** (M2) the clinical severity of an inflammatory **disease**, age-related **tissue disorder**, a **disorder** characterized by accelerated or abnormal **tissue** aging, an autoimmune **disease**, in a patient;

(2) **determining** (M3) the clinical status of a joint region or a patient;

(3) monitoring (M4) regenerative or degenerative activity within a joint region of a patient;

(4) **determining** (M5) the effective dose of an anti-inflammatory agent in a subject;

(5) **determining** (M6) the ability of a patient to respond to an anti-inflammatory agent;

(6) **determining** (M7) joint **tissue** deterioration, including deterioration associated with **disease** or age; and

(7) **determining** (M8) joint **tissue** aging, including premature aging associated with **disease**.

USE - The methods are useful for **detecting**, **diagnosing** and **determining** a predisposition for, or monitoring inflammatory **disease** (e.g. rheumatoid arthritis, lupus erythematosus, gout, fibromyalgia syndrome, polymyalgia rheumatica, psoriasis, bacterial infection, viral infection or fungal infection), an age-related **tissue disorder**, a **disorder** characterized by accelerated or abnormal **tissue** aging, an autoimmune **disease** (e.g. rheumatoid arthritis, lupus erythematosus and non-inflammatory monoarthritis, and psoriasis), or a predisposition to a **disease** resulting in cartilage degradation or degeneration.

Dwg.0/17

L11 ANSWER 12 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-102247 [09] WPIDS
CROSS REFERENCE: 2001-502527 [55]
DOC. NO. CPI: C2003-025682
TITLE: Producing bone ex vivo, by obtaining osteogenic/bone precursor cells, culturing cells with osteogenic growth factors, and maintaining cultures at cell densities that allow formation of bone cell spheroids.
DERWENT CLASS: A96 B04 D16
INVENTOR(S): KALE, S; LONG, M W
PATENT ASSIGNEE(S): (KALE-I) KALE S; (LONG-I) LONG M W; (UNMI) UNIV MICHIGAN
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002127711	A1	20020912	(200309)*		39
US 6811776	B2	20041102	(200472)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

US 2002127711	A1	US 2000-753043	20001227
US 6811776	B2	US 2000-753043	20001227

PRIORITY APPLN. INFO: US 2000-753043 20001227
AN 2003-102247 [09] WPIDS
CR 2001-502527 [55]
AB US2002127711 A UPAB: 20041122
NOVELTY - Producing (M1) bone ex vivo, comprises obtaining an osteogenic cell or bone precursor cell, culturing the cell under serum free conditions in the presence of one or more osteogenic growth factors, and maintaining the cell cultures at cell densities that allow the formation of a bone cell spheroid (the bone is formed by the cells within the bone cell spheroid).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) providing (M2) bone tissue to a mammal, comprises obtaining a bone cell spheroid and implanting the bone cell spheroid into the mammal;

(2) using (M3) bone for bone repair in a subject, comprises:

(a) obtaining and culturing the bone cell under serum free conditions as in M1;

(b) contacting the cell with a recombinant vector that expresses a protein that enhances bone cell spheroid formation;

(c) maintaining the cell cultures at cell-densities that allow the formation of a bone cell spheroid (bone is formed by cells within the bone cell spheroid);

(d) removing the cellular elements from the ex vivo formed bone; and

(e) using the bone to effect repair;

(3) identifying (M4) a gene involved in bone formation, bone repair and/or bone disease, comprises:

(a) obtaining, culturing and maintaining the bone precursor cell as in M1; and

(b) identifying a gene that is over or under expressed during the formation of a bone cell spheroid and not so expressed in the untreated osteogenic or bone precursor cell;

(4) identifying (M5) a modulator of bone formation, bone repair and/or bone disease, comprises:

(a) obtaining and culturing the bone cell as in M1;

(b) **measuring** bone cell spheroid formation; and

(c) comparing the formation of bone cell spheroid with that observed in the absence of the modulator;

(5) producing (M6) a modulator of bone formation, bone repair, and/or bone disease, comprises:

(a) obtaining and culturing the bone cell;

(b) **measuring** and comparing the bone cell spheroid formation as in M5; and

(c) producing a modulator so identified; and

(6) a bone cell spheroid made by a process comprising:

(a) of obtaining an osteogenic cell or bone precursor cell;

(b) culturing the cell under serum free conditions in the presence of one or more osteogenic growth factors; and

(c) maintaining the cell cultures at cell densities that allow the formation of a bone cell spheroid, where bone is formed by cells within the bone cell spheroid.

ACTIVITY - Tranquilizer; Vulnerary; Osteopathic.

No biological data given.

MECHANISM OF ACTION - None given.
USE - M1 Is useful for producing bone ex vivo, where the osteogenic cell or bone precursor cell is of human, bovine, equine, canine, feline, murine, rat or chick origin. M2 is useful for providing bone **tissue** to a mammal, where the mammal has a bone **disease** such as osteoporosis, vitamin D deficiency, osteotitis deformans, Von Recklinghausen's **disease**. The obtained bone is useful for bone repair (claimed), bone fractures, breaks or other traumas in a subject. Dwg.0/10

L11 ANSWER 13 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-414103 [44] WPIDS
CROSS REFERENCE: 1997-385296 [35]; 2001-606375 [69]; 2004-031977 [03]
DOC. NO. NON-CPI: N2002-325530
DOC. NO. CPI: C2002-116975
TITLE: Producing morphogenic analog having **osteogenic protein-1** like biological activity useful for therapeutic purposes, involves use of a portion of atomic co-ordinates defining three-dimensional structure of the protein.
DERWENT CLASS: B05 D16 S03 S05 T01
INVENTOR(S): CARLSON, W D; GRIFFITH, D L; KECK, P C; RUEGER, D C; SAMPATH, K T
PATENT ASSIGNEE(S): (CARL-I) CARLSON W D; (GRIF-I) GRIFFITH D L; (KECK-I) KECK P C; (RUEG-I) RUEGER D C; (SAMP-I) SAMPATH K T
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002028453	A1	20020307	(200244)*		128

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2002028453	A1	CIP of	US 1996-589552	19960122
		Cont of	US 1997-786284	19970122
			US 2001-791946	20010222

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 2002028453	A1	Cont of	US 6273598

PRIORITY APPLN. INFO: US 1997-786284 19970122; US 1996-589552 19960122; US 2001-791946 20010222
AN 2002-414103 [44] WPIDS
CR 1997-385296 [35]; 2001-606375 [69]; 2004-031977 [03]
AB US2002028453 A UPAB: 20040112
NOVELTY - Producing (M1) a morphogenic analog having **osteogenic protein-1** (**OP-1**) like biological activity, involves providing a molecular model defining a three-dimensional (3D) shape representative of at least a portion of human

OP-1, identifying a candidate analog having a 3D shape corresponding to the 3D shape representative of the portion of human **OP-1**, and producing the candidate analog identified.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a computer system (I) comprising a memory having disposed in it atomic X-ray crystallographic co-ordinates defining at least a portion of human **OP-1**, and a processor in electrical communication with the memory, where the processor comprises a process which generates a molecular model having a 3D shape representative of at least a portion of human **OP-1**;

(2) producing (M2) a morphogen analog that modulates an **OP-1** mediated biological effect, involves providing a computer memory atomic X-ray crystallographic co-ordinates defining at least a portion of human **OP-1**, generating with a processor a molecular model having a 3D shape and a solvent accessible surface representative of at least a portion of human **OP-1**, identifying a candidate morphogen analog having a 3D structure shape and a solvent accessible surface corresponding to the 3D shape and the solvent accessible surface of at least a portion of human **OP-1**, producing the candidate morphogen analog identified, and **determining** whether the candidate morphogen analog produced modulates the **OP-1** mediated biological effect; and

(3) a compound (II) that modulates an **OP-1** mediated biological effect produced by M1 or M2.

ACTIVITY - Vulnerary; antiinflammatory.

No biological data is given.

MECHANISM OF ACTION - Modulator of **OP-1** mediated biological effect (claimed); stimulator of osteocalcin synthesis in osteoblast cultures; inhibitor of immune/inflammatory response-mediated tissue damage and scar tissue formation following an injury.

No biological data is given.

USE - M1 is useful for producing a morphogenic analog having **OP-1** like biological activity (claimed). (II) is useful for repairing **diseased** or damaged mammalian **tissue**, to prevent or inhibit immune/inflammatory response-mediated **tissue** damage and scar **tissue** formation following an injury.

ADVANTAGE - (II) has greater solubility and/or stability in aqueous buffers than native dimeric hOP-1.

Dwg.0/16

L11 ANSWER 14 OF 41 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2002288698 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12028617

TITLE: Healing course of primate ulna segmental defects treated with **osteogenic protein-1**.

AUTHOR: Cook Stephen D; Salkeld Samantha L; Patron Laura P; Sargent M Catherine; Rueger David C

CORPORATE SOURCE: Department of Orthopedic Surgery, Tulane University School of Medicine, New Orleans, Louisiana 70112, USA.. scook2@tulane.edu

SOURCE: Journal of investigative surgery : official journal of the Academy of Surgical Research, (2002 Mar-Apr) 15 (2) 69-79. Journal code: 8809255. ISSN: 0894-1939.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020528
Last Updated on STN: 20021031
Entered Medline: 20021030

AB Twelve African green monkeys were implanted with recombinant human **osteogenic protein-1** (rhOP-1) placed on a bovine bone-derived Type I collagen carrier to characterize healing in an ulna segmental bone defect model at 1, 3, 12, and 20 weeks postoperative. Defect healing was evaluated by plain film radiography, computed tomography (CT), magnetic resonance imaging (MRI), bone mineral density (BMD), and histologic analysis. Radiographically, new bone formation was observed as early as 3 weeks postoperative. By 6 weeks, new bone was visible in five of six defects. Increased **quantity** and mineralization of the new bone were apparent by 12 weeks. Reformation of the medullary cavity with appearance of marrow elements was demonstrated by CT and MRI at 20 weeks. BMD studies revealed a significant increase in the presence of bone with time. Histology at 1 week demonstrated that the implant material was well contained in the defect, and a proliferation of cells occurred at the defect borders. At 3 weeks cell proliferation continued and cell phenotype differentiation was recognized. By 12 weeks substantially less residual carrier was found in the defects, and calcifying tissues with plump chondrocytes, osteoblasts, and immature woven bone were observed. Areas of lamellar and woven bone were identified at 12 weeks, with advanced remodeling and revascularization observed at 20 weeks. The use of osteoinductive implants may provide an alternative to autologous and allogeneic bone **tissue** in the therapeutic approach to bone defects and promotion of fusion by eliminating the donor site morbidity associated with autogenous bone and the decreased efficacy and potential for **disease** transmission associated with allogeneic bone.

L11 ANSWER 15 OF 41 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002032624 EMBASE
TITLE: **Bmp-7** regulates chemokine, cytokine, and hemodynamic gene expression in proximal tubule cells.
AUTHOR: Gould S.E.; Day M.; Jones S.S.; Doral H.
CORPORATE SOURCE: Dr. S.E. Gould, Curis, Inc., 61 Moulton Street, Cambridge, MA 02138, United States. sgould@curis.com
SOURCE: Kidney International, (2002) 61/1 (51-60).
Refs: 48
ISSN: 0085-2538 CODEN: KDYIA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
026 Immunology, Serology and Transplantation
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background. Proximal tubule epithelial cells (PTEC) play a central role in the response of the kidney to insult by virtue of their production of chemokines and cytokines that signal an inflammatory response.

Bone morphogenic protein-7 (BMP-7/ OP-1), a member of the transforming growth factor-β (TGF-β) superfamily, has previously been demonstrated to reduce macrophage infiltration and **tissue** damage in animal models of acute and chronic renal failure. The present study was designed to define the molecular mechanism of **BMP-7** action in human PTEC. Methods. Expression of **BMP-7** in the adult mouse kidney was **determined** indirectly through X-gal staining of heterozygous **BMP-7**/lacZ mice in combination with cell-type specific markers. Primary human PTEC were cultured in the presence of the pro-inflammatory cytokine, tumor necrosis factor-tα (TNF-α), with and without **BMP-7**. RNA isolated from these two populations was then used to identify differentially regulated genes via gene-array analysis. Modulation of potential target genes was subsequently confirmed through ELISA and/or **quantitative** PCR. Results. Expression from the **BMP-7**/lacZ transgene was **detected** in the collecting duct, thick ascending limb, distal convoluted tubule, and podocytes within glomeruli. No expression was **detected** within PTEC; however, these cells were found to express mRNA for BMP receptors including, ActR-I, BMPR-IA, ActR-II, ActR-IIB, and BMPR-II. **BMP-7** significantly reduced TNF-α stimulated increases in mRNA for the pro-inflammatory genes, interleukin-6 (IL-6) and interleukin-1β (IL-1 β), and the chemoattractants monocyte chemotactic protein-1 (MCP-1) and interleukin-8 (IL-8) in primary human PTEC. In addition, **BMP-7** also reduced the expression of mRNA for endothelin-2 (ET-2), a vasoconstrictor, and increased the expression of mRNA for heme oxygenase-1 (HO-1), a vasodilator, although the latter was not statistically significant. In experiments designed to examine MCP-1 and IL-6 protein levels in response to additional TGF-β superfamily members, TGF-β1 was unable to mimic the effects of **BMP-7** in reducing IL-6 production. However, the closely related BMP-6 exhibited similar properties to those of **BMP-7**. Each of the factors reduced MCP-1 expression. Conclusions. **BMP-7** represses the basal and TNF-α-stimulated expression of the pro-inflammatory cytokines IL-6 and IL-1β, the chemokines MCP-1 and IL-8, and the vasoconstrictor ET-2 in PTEC. This data are consistent with the in vivo observations that **BMP-7** administration in a model of chronic and acute renal failure results in a reduction in the infiltration of macrophages in the renal interstitium. Taken together, these observations suggest that **BMP-7** may be a novel therapeutic agent for kidney **disorders** involving inflammation and ischemic damage of PTEC.

L11 ANSWER 16 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-502527 [55] WPIDS
CROSS REFERENCE: 2003-102247 [09]
DOC. NO. NON-CPI: N2001-372696
DOC. NO. CPI: C2001-151140
TITLE: Producing mammalian bone ex vivo for use in bone repair, comprises culturing an osteogenic cell in the presence of osteogenic growth factors.
DERWENT CLASS: A96 B04 D16 D22 P32 P34 S03
INVENTOR(S): KALE, S; LONG, M W
PATENT ASSIGNEE(S): (UNMI) UNIV MICHIGAN
COUNTRY COUNT: 24

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001048148	A1	20010705	(200155)*	EN	85
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR					
W: AU CA JP					
AU 2001024666	A	20010709	(200164)		
EP 1242577	A1	20020925	(200271)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR					
JP 2003518379	W	20030610	(200339)		116
US 2004225374	A1	20041111	(200475)		
US 2004229353	A1	20041118	(200477)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001048148	A1	WO 2000-US35720	20001227
AU 2001024666	A	AU 2001-24666	20001227
EP 1242577	A1	EP 2000-988458	20001227
		WO 2000-US35720	20001227
JP 2003518379	W	WO 2000-US35720	20001227
		JP 2001-548661	20001227
US 2004225374	A1 Provisional	US 1999-173350P	19991228
	Div ex	US 2000-753043	20001227
		US 2004-862972	20040608
US 2004229353	A1 Provisional	US 1999-173350P	19991228
	Div ex	US 2000-753043	20001227
		US 2004-862997	20040608

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001024666	A Based on	WO 2001048148
EP 1242577	A1 Based on	WO 2001048148
JP 2003518379	W Based on	WO 2001048148

PRIORITY APPLN. INFO: US 1999-173350P 19991228; US 2000-753043 20001227; US 2004-862972 20040608; US 2004-862997 20040608

AN 2001-502527 [55] WPIDS

CR 2003-102247 [09]

AB WO 200148148 A UPAB: 20041203

NOVELTY - Producing bone ex vivo, comprises culturing an osteogenic cell under serum free conditions in the presence of osteogenic growth factors and maintaining the cell cultures at densities that allow formation of a bone cell spheroid.

DETAILED DESCRIPTION - Producing (M1) bone ex vivo, comprises:

(a) obtaining an osteogenic cell or bone precursor cell;

(b) culturing the cell under serum free conditions in the presence of one or more osteogenic growth factors; and

(c) maintaining the cell cultures at cell-densities that allow the formation of a bone cell spheroid, where bone is formed by cells within

the bone cell spheroid; and

(d) removing the cellular elements from the formed bone cell spheroid and using resulting bone in vivo.

INDEPENDENT CLAIMS are also included for the following:

(1) providing (M2) bone tissue to a mammal, comprises obtaining a bone cell spheroid and implanting the bone cell spheroid into the mammal;

(2) producing (M3) bone ex vivo, comprising:

(a) obtaining an osteogenic cell or bone precursor cell;

(b) culturing the cell under serum free conditions in the presence of one or more osteogenic growth factors;

(c) contacting the cell with a recombinant vector that directs the expression of a protein that modifies bone cell spheroid formation; and

(d) initiating the cell cultures at cell-densities that allow the formation of a bone cell spheroid, where the bone is formed with the bone cell spheroid;

(3) identifying (M4) a gene involved in bone formation, bone repair and/or bone disease, comprises:

(a) obtaining an osteogenic cell or bone precursor cell;

(b) culturing the cell under serum free conditions in the presence of one or more growth factors of the TGF- beta (transforming growth factor beta) gene superfamily;

(c) maintaining the cell cultures at cell-densities that allow the formation of a bone cell spheroid; and

(d) identifying a gene that is over or under expressed during the formation of a bone cell spheroid and not so expressed in the untreated osteogenic or bone precursor cell;

(4) identifying a modulator of bone formation, bone repair and/or bone disease, comprises:

(a) obtaining an osteogenic cell or bone precursor cell;

(b) culturing the cell under serum free conditions in the presence of a candidate modulator in the presence or absence of one or more osteogenic growth factors;

(c) **measuring** bone cell spheroid formation;

(d) comparing the formation of bone cell spheroid with that observed in the absence of the modulator; and

(e) producing the identified modulator; and

(5) a bone cell spheroid produced by (M1).

ACTIVITY - Osteopathic. No biodata is provided.

MECHANISM OF ACTION - Gene therapy.

USE - The method is useful for producing bone ex vivo. The bone can be used for bone repair in a subject, which comprises obtaining an osteogenic cell or bone precursor cell, culturing the cell under serum free conditions in the presence of one or more osteogenic growth factors, contacting the cell with a recombinant vector that expresses a protein that enhances bone cell spheroid formation, maintaining the cell cultures at cell-densities that allow the formation of a bone cell spheroid, where bone is formed by cells within the bone cell spheroid, removing the cellular elements from the ex vivo formed bone and using the bone to effect repair (claimed). Examples of human conditions that would benefit from the new bone repair technology, include a fracture, osteogenesis imperfecta, osteoporosis and bone reconstruction resulting from traumatic injury as a consequence of cancer surgery or a birth defect.

Dwg.0/10

L11 ANSWER 17 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-266158 [27] WPIDS

DOC. NO. CPI: C2001-080616
TITLE: Improving tissue inductive capability of morphogenic protein at target locus in mammal involves administering morphogenic protein with a hormone and its soluble receptor, to the target locus.
DERWENT CLASS: B04 D16
INVENTOR(S): LEE, J C; YEH, L C
PATENT ASSIGNEE(S): (STYC) STRYKER CORP
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001023563	A2	20010405	(200127)*	EN	49
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 2000076191	A	20010430	(200142)		
EP 1220909	A2	20020710	(200253)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2003510338	W	20030318	(200321)		80
US 6696410	B1	20040224	(200415)		
US 2004138128	A1	20040715	(200447)		
AU 773990	B2	20040610	(200467)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001023563	A2		WO 2000-US26528	20000927
AU 2000076191	A		AU 2000-76191	20000927
EP 1220909	A2		EP 2000-965478	20000927
			WO 2000-US26528	20000927
JP 2003510338	W		WO 2000-US26528	20000927
			JP 2001-526945	20000927
US 6696410	B1	Provisional	US 1999-156261P	19990927
			US 2000-672224	20000927
US 2004138128	A1	Provisional	US 1999-156261P	19990927
		Div ex	US 2000-672224	20000927
			US 2004-753916	20040107
AU 773990	B2		AU 2000-76191	20000927

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000076191	A	Based on	WO 2001023563
EP 1220909	A2	Based on	WO 2001023563
JP 2003510338	W	Based on	WO 2001023563
US 2004138128	A1	Div ex	US 6696410
AU 773990	B2	Previous Publ.	AU 2000076191
		Based on	WO 2001023563

PRIORITY APPLN. INFO: US 1999-156261P 19990927; US 2000-672224 20000927; US 2004-753916 20040107
AN 2001-266158 [27] WPIDS

Searcher : Shears 571-272-2528

AB WO 200123563 A UPAB: 20010518
NOVELTY - Improving (M1) the tissue inductive capability of a morphogenic protein at a target locus in a mammal involves administering to the target locus the morphogenic protein, a hormone, and a soluble receptor of the hormone, where the morphogenic protein's capability to induce tissue formation when accessible to the progenitor cell in the mammal, is enhanced by the hormone-receptor combination.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition (I) for inducing tissue formation in a mammal comprising a morphogenic protein, a hormone, and a soluble receptor of the hormone, where the morphogenic protein's capability to induce tissue formation when accessible to the progenitor cell in the mammal, is enhanced by the hormone-receptor combination; and

(2) a kit (II) for inducing tissue formation in a mammal containing a morphogenic protein, a hormone, and a soluble receptor of the hormone, where the morphogenic protein's capability to induce tissue formation when accessible to the progenitor cell in the mammal, is enhanced by the hormone-receptor combination.

ACTIVITY - Osteopathic; antiulcer; antirheumatoid; antiarthritic; antipsoriatic; antiinflammatory;

MECHANISM OF ACTION - Osteogenic activity of morphogenic protein enhancer; gene therapy; local tissue formation or regeneration stimulator; progenitor cell proliferation and/or differentiation inducer.

To investigate whether IL-6/R stimulates the expression of **OP-1** receptors on FRC cells, the mRNA levels of three bone morphogenic protein (BMP) type I receptors (BMPR-IA, BMPR-IB, and ActR-I) and one BMP type II receptor (BMPR-II) were **measured** by Northern blot analysis. Briefly, confluent FRC cells were treated for 48 hours with (i) a vehicle; (ii) 200 ng/ml osteogenic protein (**OP**)-**1**, (iii) 40 ng/ml IL-6 and 50 ng/ml sIL-6R; or (iv) 200 ng/ml **OP-1**, 40 ng/ml IL-6, ad 50 ng/ml sIL-6R. Total RNA was isolated. Northern blots were prepared and probed with 32P-labeled cDNA encoding for the various BMPRs. These probes hybridized only to mRNA. The radioactive bands were **detected** and **quantified**. To normalize the band intensity of the BMPR bands, the blots were also probed with an oligonucleotide for the 18S rRNA. The mRNA levels in control FRC cells, **OP-1**-treated cells, **OP-1**-treated cells, IL-6/R-treated cells, and (**OP-1**+IL-6R)-treated cells were compared. The data showed that **OP-1** did not affect the mRNA level of the type I receptors, but stimulated the BMPR-II mRNA level by about 2.2 fold. Likewise, IL-6/R did not alter the mRNA expression level of the type I receptors, but increased the BMPR-II mRNA level by about 1.5-fold. In the presence of **OP-1** and IL-6/R, the mRNA level of the type I receptors was not significantly changed, however, the BMPR-II mRNA level was almost 3-fold higher than the control. These results suggest that IL-6/R can stimulate the osteogenic activity of **OP-1** by elevating BMPR-II mRNA expression.

USE - Improving the **tissue** inductive capability of a morphogenic protein at a target locus e.g. a jaw bone defect such as a fracture, a non-union fracture, a critical or non-critical size defect, an osteochondral defect, a fusion or a bony void, in a mammal. Alternately, the target locus has a **tissue** (cartilage or soft **tissue** or neural **tissue**) degenerative condition (claimed). Nucleic acid constructs comprising nucleic acids encoding morphogenic proteins can also be employed in the above mentioned methods for treating the stated

defects. The pharmaceutical compositions, morphogenic devices are useful for treating **tissue** injuries, **tissue** degeneration and other **tissue diseases**. The morphogenic devices may be implanted in or around a joint for use in cartilage and soft **tissue** repair or in surrounding nervous system-associated **tissue** for use in neural regeneration and repair. The morphogenic devices and compositions are useful for treating congenital **diseases**, and developmental abnormalities of cartilage, bone and other **tissues**. An osteogenic device (a matrix comprising allogenic bone) can be implanted at a site in need of bone replacement to accelerate allograft repair and incorporation in a mammal. The compositions and devices may also be useful for treating inflammatory joint **diseases** such as rheumatoid and psoriatic arthritis, bursitis, ulcerative colitis, Whipple's **disease**, ankylosing spondylits, systemic lupus erythematosus, rheumatic fever, amyloidosis, thrombotic thrombocytopenic purpura and relapsing polychondritis.

ADVANTAGE - The osteogenic compositions permit predictable bone, ligament and/or cartilage formation to be obtained using less osteogenic protein to achieve at least about the same extent of bone or cartilage formations.

Dwg.0/5

L11 ANSWER 18 OF 41 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001122541 EMBASE

TITLE: **Bone morphogenetic protein-7** modulates genes that maintain the vascular smooth muscle cell phenotype in culture.

AUTHOR: Dorai H.; Sampath T.K.

CORPORATE SOURCE: Dr. H. Dorai, Curis Inc., 21 Erie Street, Cambridge, MA 02139, United States. hdorai@curis.com

SOURCE: Journal of Bone and Joint Surgery - Series A, (2001) 83/SUPPL. 1 (S17O-S178).
Refs: 46
ISSN: 0021-9355 CODEN: JBJSA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT:
009 Surgery
018 Cardiovascular Diseases and Cardiovascular Surgery
021 Developmental Biology and Teratology
029 Clinical Biochemistry
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Background: The vasculature is an important component in the musculoskeletal system, and vascularization is a key event in the development of normal cartilage and bone formation. Blood vessels deliver nutrients, oxygen, and precursor cells to maintain the structural and functional integrity of joints and soft and hard **tissues**. Therefore, agents that help to inhibit proliferation and retain the phenotype of vascular smooth muscle cells (SMCs) are of critical importance. In this study, we examined the capacity of **bone morphogenetic protein-7** (**BMP-7**) to inhibit the proliferation of SMCs and maintain their phenotype. Methods: A thymidine-incorporation assay was used to monitor the proliferative activity of SMCs on stimulation with platelet-derived

growth factor (PDGF) and transforming growth factor-beta (TGF-β), agents known to be stimulatory for these cells. Reverse transcriptase-polymerase chain reaction (RT-PCR), Northern blot analysis, and enzyme-linked immunosorbent assay (ELISA) were used to monitor the modulation of various genes and gene products. Immunolocalization of SMC specific markers was also performed. Results: **BMP-7** inhibited both serum-stimulated and growth factor-induced (PDGF-BB and TGF-β1) SMC growth, as **measured** by (3)H-thymidine uptake and cell number, in primary human aortic smooth muscle (HASM) cell cultures. The addition of **BMP-7** stimulated the expression of developmentally regulated as well as SMC-specific markers, namely, Id-1 and Id-2, α-actin, and SMC-specific heavy-chain myosin, as examined by semiquantitative and **quantitative** RT-PCR and by Northern blot analysis. Additionally, **BMP-7** exhibited anti-inflammatory activity by downregulating intercellular adhesion molecule-1 (ICAM-1) expression. The collagen type III/I ratio that becomes lower with the transdifferentiation of SMCs into myofibroblasts is maintained in **BMP-7**-treated cultures compared with untreated controls. Studies on the mechanism of action indicate that **BMP-7** treatment induces cyclin-dependent kinase-2 inhibitor, p21, which was inhibited during PDGF-BB-induced proliferation of SMCs. Finally, **BMP-7** upregulates the expression of the inhibitory Smads, Smad6 and Smad7, which are known to inhibit TGF-β superfamily signaling. Conclusions: These results suggest that **BMP-7** maintains the expression of the vascular SMC phenotype. Thus, **BMP-7** may prevent vascular proliferative **disorders** and potentially could act as a palliative agent following damage to the vasculature. Clinical Relevance: In musculoskeletal **disorders** in which the vasculature plays an important role, **BMP-7** may be of benefit as an anti-inflammatory and anti-proliferative agent for vascular endothelium and help maintain vascular integrity.

L11 ANSWER 19 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-549143 [50] WPIDS
DOC. NO. CPI: C2000-163961
TITLE: New pancreatic progenitor cells for regulating the expression of insulin and other beta cell components by differentiating into glucose-responsive, insulin-secreting cells and for treating type 1 diabetes mellitus.
DERWENT CLASS: B04 D16
INVENTOR(S): FUNG, B; KAGAN, D; PANG, K
PATENT ASSIGNEE(S): (ONTO-N) ONTOGENY INC; (CURI-N) CURIS INC
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000047720	A2	20000817	(200050)*	EN	104

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000036979	A	20000829	(200062)
US 6326201	B1	20011204	(200203)
EP 1175487	A2	20020130	(200216) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI			
JP 2002538779	W	20021119	(200281) 134

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000047720	A2	WO 2000-US3419	20000210
AU 2000036979	A	AU 2000-36979	20000210
US 6326201	B1 Provisional	US 1999-119576P	19990210
	Provisional	US 1999-142305P	19990702
	Provisional	US 1999-171338P	19991221
		US 2000-499362	20000210
EP 1175487	A2	EP 2000-915758	20000210
		WO 2000-US3419	20000210
JP 2002538779	W	JP 2000-598620	20000210
		WO 2000-US3419	20000210

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000036979	A Based on	WO 2000047720
EP 1175487	A2 Based on	WO 2000047720
JP 2002538779	W Based on	WO 2000047720

PRIORITY APPLN. INFO: US 1999-171338P 19991221; US 1999-119576P 19990210; US 1999-142305P 19990702; US 2000-499362 20000210

AN 2000-549143 [50] WPIDS

AB WO 200047720 A UPAB: 20001010

NOVELTY - A substantially pure population of viable pancreatic progenitor cells (PPC) characterized by expression of a transcription factor that regulates expression of insulin and other beta cell components (PDX1) and able to differentiate into glucose-responsive, insulin-secreting cells, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a cellular composition comprising, as the cellular component, a substantially pure population of viable PCC capable of proliferation and/or differentiation in a culture medium;

(2) a cellular composition comprising 75 % progenitor cells being isolated from pancreatic ductal epithelium or the progeny of them, which are capable of self-regeneration in a culture medium;

(3) a cellular composition comprising viable PCC capable of self-regeneration in a culture medium and differentiation to members of the pancreatic lineages;

(4) a cellular composition comprising PPC capable of self-regeneration in a culture medium and differentiation to members of the pancreatic lineages, with fewer than 20 % of lineage committed cells;

(5) isolating (A) progenitor cells comprising:

(i) obtaining pancreatic ductal cells;
(ii) culturing the pancreatic cells in nutrient medium; and
(iii) isolating a population of progenitor cells from the culture;
(6) a cellular composition as in (2), where the cells are isolated (B) by:
(a) obtaining dissociated epithelial cells from pancreatic ducts;
(b) culturing, as a monolayer, the epithelial cells in nutrient medium to expand pancreatic progenitors from the epithelial cell monolayer; and
(c) isolating the progenitor cells from the culture;
(7) stimulating (C) the ex vivo proliferation of mammalian pancreatic beta -islet cells, comprising preparing a primary culture of mammalian pancreatic cells and contacting them with a cyclic AMP (cAMP) agonist to induce differentiation to beta -islet cells;
(8) stimulating (D) the ex vivo proliferation of human adult pancreatic beta cells comprising preparing a monolayer culture of primary human adult pancreatic cells and culturing the cells with a growth factor and a cAMP agonist to induce the primary culture to produce insulin-producing cells;
(9) treating (E) a subject suffering from or at risk of developing, type 1 diabetes mellitus comprising:
(a) preparing a primary culture of human adult pancreatic cells;
(b) contacting the culture with a reagent containing a cAMP agonist to induce the culture to produce insulin-producing cells;
(c) harvesting the adult pancreatic cells; and
(d) transplanting the cells of (c) in a subject;
(10) producing, proliferating and differentiating (F) human adult pancreatic islet cells in clinically useful **quantities** comprising:
(a) seeding a bioreactor with a human pancreatic cell culture;
(b) perfusing the bioreactor with a complete growth medium supplemented with cAMP agonist to induce cells in the bioreactor to proliferate and differentiate into insulin-secreting cells; and
(c) harvesting insulin-secreting cells from the bioreactor.

ACTIVITY - Antidiabetic. Functional beta cells derived from the non-adherent portion of a differentiated pancreatic duct monolayer were implanted into streptozotocin (STZ)-treated diabetic mice. Insulin containing pellets were then implanted subcutaneously to stabilize the blood glucose and create a more stable environment for cell implantation. Within 48 hours of pellet implantation, the fasting blood glucose of the animals was reduced from 180 - 380 mg/dl blood glucose to less than 50 mg/dl. Cells were implanted under the renal capsule. An animal that received duct-derived cells showed a transient rescue of the diabetic state (4 - 5 day lowering of greater than 150 mg/dl blood glucose before rebounding to pre-implant blood glucose levels).

MECHANISM OF ACTION - Insulin expression regulator. No biological data is given.

USE - Adult pancreatic cells that are isolated, proliferated, differentiated ex vivo and induced to produce insulin in vivo are used to treat a subject suffering from or at risk of developing, type 1 diabetes mellitus by transplanting the cells into the subject (claimed). The progenitor cells can be used in the treatment or prevention of a variety of pancreatic **disorders**, both exocrine and endocrine.
Populations of differentiated pancreatic cells can be produced by the progenitor cells for repair subsequent to partial pancreatectomy (excision of a portion of the pancreas) or for regenerating or replacing pancreatic

tissue loss due to pancreatolysis e.g. destruction of pancreatic **tissue**. The progenitor cells and their progeny can be used to **screen** compounds for their ability to modulate growth, proliferation or differentiation of distinct progenitor cell populations from pancreatic ductal epithelial culture.

ADVANTAGE - The expansion and differentiation of a pancreatic stem/progenitor cell to create functional beta cells in vitro obviates the need for physical dissociation of tissue in order to obtain islets. The process has potential for greater reproducibility and control.

Dwg.0/40

L11 ANSWER 20 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-505971 [45] WPIDS
DOC. NO. CPI: C2000-151905
TITLE: Differentiating human pre-adipocyte cells into adipocyte cells for the study of diabetes and obesity and to assay for therapeutic agents for treating these disorders.
DERWENT CLASS: B04 D16
INVENTOR(S): HALVORSEN, Y C; WILKISON, W O
PATENT ASSIGNEE(S): (ZENB-N) ZEN BIO INC
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000044882	A2	20000803	(200045)*	EN	56
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA CN JP US					
US 6153432	A	20001128	(200063)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000044882	A2	WO 2000-US2208	20000128
US 6153432	A	US 1999-240029	19990129

PRIORITY APPLN. INFO: US 1999-240029 19990129
AN 2000-505971 [45] WPIDS
AB WO 200044882 A UPAB: 20010410

NOVELTY - A method (I) for the differentiation of human pre-adipocytes isolated from adipose tissue into adipocytes, is new. The method comprises culturing the cells in media containing combinations of glucose, cyclic adenosine monophosphate (AMP) inducers, glucocorticoids and insulin (or analogs) and agonists of PPAR gamma (undefined) and RXR (undefined).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method (I) for differentiating human pre-adipocytes into adipocytes, comprising:

(a) plating isolated human pre-adipocytes at a density of 25000 - 30000 cells/cm2 in a pre-adipocyte medium (Ia) comprising a cell culture medium containing 1.0 - 4.5 g/L glucose and 0 - 15% fetal serum;

(b) incubating the cells at about 37 deg. C for 4 - 48 hours until the cells are 95 - 100% confluent;

(c) replacing the pre-adipocyte medium with a differentiation medium

(Ib) comprising a cell culture medium containing 1.0 - 4.5 g/L glucose, 1 - 15% fetal serum, a cyclic adenosine monophosphate (AMP) inducer, 100 nM - 1 micro M insulin or insulin analog, 16 nM - 1 micro M glucocorticoid and a PPAR gamma (undefined) agonist or RXR (undefined) agonist to stimulate differentiation of the human pre-adipocytes and a vehicle;

(d) incubating the cells at 37 deg. C for 2 - 4 days;

(e) replacing the differentiation medium with an adipocyte medium (Ic) comprising a cell culture medium containing 1.0 - 4.5 g/L glucose, 0 - 15% fetal serum, 100 nM - 1 micro M insulin or insulin analog and 16 nM - 1 micro M glucocorticoid, but no cAMP, PPAR gamma or RXR agonist to stimulate the differentiation of the adipocytes; and

(f) incubating the cells at 37 deg. C for 1 -2 weeks and refeeding the cells with the adipocyte medium every 3 - 4 days (the pre-adipocyte, differentiation and adipocyte media are maintained at a pH of 7.0 - 7.6 when in contract with the cells;

(2) a method (II) for **determining** the ability of a compound to affect the differentiation of pre-adipocytes to adipocytes, comprising:

(i) carrying out steps (a) to (f) from method (I);

(ii) **determining** the number or percentage of differentiated cells in the culture obtained from step (f) fed at step (c) with the differentiation medium containing the compound;

(iii) **determining** the number or percentage of differentiated cells in the culture obtained from step (f) fed at step (c) with the differentiation medium containing a vehicle alone; and

(iv) comparing the number or percentage of differentiated cells from steps (ii) and (iii) ((Ia), (Ib) and (Ic) are maintained at a pH of 7.0 - 7.6 when in contract with the cells);

(3) a method (III) for **determining** the ability of a compound to act as a PPAR gamma antagonist, comprising:

(i) carrying out steps (a) to (c) from method (I), however in step (c) no RXR agonist is used and the amount of PPAR gamma used is only sufficient to stimulate half-maximal differentiation of the pre-adipocytes;

(ii) carrying out step (d) and (e) from (I), however in step (e), (Ib) does not contain the cyclic AMP inducer or PPAR gamma and/or RXR agonists to stimulate the differentiation of the pre-adipocytes;

(iii) incubating the cells at 37 deg. C for 1 week and refeeding the cells with the medium from step (e) at least once;

(iv) **determining** the number or percentage of differentiated cells in the culture obtained from step (f) fed at step (c) with the differentiation medium containing the compound;

(v) **determining** the number or percentage of differentiated cells in the culture obtained from step (f) fed at step (c) with the differentiation medium containing a vehicle alone; and

(vi) comparing the number or percentage of differentiated cells from steps (iv) and (v) ((Ia), (Ib) and (Ic) are maintained at a pH of 7.0 - 7.6 when in contract with the cells);

(4) a method (IV) for **determining** the ability of a compound to act as an insulin analog, comprising:

(i) repeating steps (a) to (f) from method (I), however the media (Ib) and (Ic) in steps (c) and (e) contain the candidate compound rather then the insulin or the insulin analog;

(ii) **determining** the number or percentage of differentiated cells in the culture obtained from step (f) fed at step (c) with the differentiation medium containing the candidate compound;

(iii) **determining** the number or percentage of differentiated cells in the culture obtained from step (f) fed at step (c) with the differentiation medium containing a vehicle alone; and

(iv) comparing the number or percentage of differentiated cells from steps (iv) and (v) ((Ia), (Ib) and (Ic) are maintained at a pH of 7.0 - 7.6 when in contract with the cells);

(5) a cultured human adipocyte (V) produced via (I);

(6) a method (VI) for identifying polypeptides secreted from cultured human adipocytes, comprising fractionating the polypeptides secreted by (V);

(7) a 3 dimensional biomaterial (VII) containing adipose tissue-derived stromal cells capable of generating an adipose tissue depot upon implantation into a host recipient prepared by a modified version (I') or (I); and

(8) a method (VIII) for grafting adipose tissue into a subject comprising introducing (VII) into the subject.

USE - The method (I) is used for stimulating differentiation of human pre-adipocytes isolated from adipose tissue into adipocytes. The differentiated adipocytes may be used to study the processes resulting in the development of diabetes obesity and/or cardiovascular disease and the method may be modified to assay for potential therapeutic agents that modulate the differentiation of pre-adipocytes to adipocytes. (I) may also be adapted to produce a 3 dimensional biomaterial (VII) containing adipose tissue-derived stromal cells capable of generating an adipose tissue depot upon implantation into a host recipient (claimed).

ADVANTAGE - (I) is a method for stimulating human pre-adipocytes to differentiate into adipocytes at a higher frequency, in a shorter period of time and with greater consistency than previous methods. The methods cause consistant differentiation in 90 - 95% of human pre-adipocytes.

Dwg.0/10

L11 ANSWER 21 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-256700 [22] WPIDS
DOC. NO. NON-CPI: N2000-190857
DOC. NO. CPI: C2000-078348
TITLE: **Diagnosing** a skeletal disorder e.g. osteoarthritis or osteoporosis, by **measuring** level of regulator or marker factors such as specific cytokines or interleukins involved in bone remodeling.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): FAZZALARI, N; FINDLAY, D; FORWOOD, M; KULIWABA, J
PATENT ASSIGNEE(S): (MEDV-N) MEDVET SCI PTY LTD
COUNTRY COUNT: 88
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000013024	A1	20000309	(200022)*	EN	42
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9957209	A	20000321	(200031)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000013024	A1	WO 1999-AU697	19990826
AU 9957209	A	AU 1999-57209	19990826

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9957209	A	Based on	WO 2000013024

PRIORITY APPLN. INFO: AU 1998-5473 19980826
AN 2000-256700 [22] WPIDS
AB WO 200013024 A UPAB: 20000508
NOVELTY - Predicting or **diagnosing** a skeletal **disorder** (SD) comprising comparing the **measured** or estimated level of mRNA expression for a regulator or marker of bone remodeling from a body **tissue** or fluid sample (S) to a standard level, is new.

USE - The method is used for **diagnosing** osteoporosis or osteoarthritis from tissue or fluid samples (containing a cellular component) by assaying for levels of specific markers in vivo and comparing the level to a standard (claimed).

ADVANTAGE - The methods can be carried out on blood or urine samples.

DESCRIPTION OF DRAWING(S) - The figure is a plot of CTR versus OCN mRNA expression and shows a significant positive correlation in the OA cancellous bone sample from the proximal femur, the control groups do not correlate.

Dwg.3/11

L11 ANSWER 22 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-205978 [18] WPIDS
CROSS REFERENCE: 2000-052937 [04]; 2004-051017 [05]
DOC. NO. CPI: C2000-063691
TITLE: New polynucleotides encoding secreted human proteins, useful for treating e.g. broken bones, craniofacial defects, peridontal disease, osteoporosis, burns, incisions or ulcers.
DERWENT CLASS: B04 D13 D16
INVENTOR(S): COLLINS-RACIE, L A; DIBLASIO-SMITH, E; JACOBS, K; LAVALLIE, E R; MCCOY, J M; MERBERG, D; TREACY, M; WIDOM, A
PATENT ASSIGNEE(S): (GEMY) GENETICS INST INC
COUNTRY COUNT: 82
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000009551	A1	20000224	(200018)*	EN	105

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

AU 9954751 A 20000306 (200030)
EP 1112285 A1 20010704 (200138) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2002538762 W 20021119 (200281) 114

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000009551	A1	WO 1999-US18117	19990810
AU 9954751	A	AU 1999-54751	19990810
EP 1112285	A1	EP 1999-941018	19990810
		WO 1999-US18117	19990810
JP 2002538762	W	WO 1999-US18117	19990810
		JP 2000-565000	19990810

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9954751	A	Based on	WO 2000009551
EP 1112285	A1	Based on	WO 2000009551
JP 2002538762	W	Based on	WO 2000009551

PRIORITY APPLN. INFO: US 1999-306111 19990506; US 1998-95880P 19980810

AN 2000-205978 [18] WPIDS
CR 2000-052937 [04]; 2004-051017 [05]
AB WO 200009551 A UPAB: 20040120
NOVELTY - New human secreted proteins are encoded by polynucleotides obtained from human adult placenta or human adult brain cDNA libraries.

DETAILED DESCRIPTION - (A) New isolated polynucleotides (PNs) comprise:

(a) one of the defined sequences (I)-(III) of 1456, 4723 and 3861 nucleotides in length, respectively, given in the specification or specified fragments of these defined as follows:

(i) comprising nucleotides 157-1356 of (I);

(ii) 1383-4490, 1485-4490 or 36345-4343 of (II);

(iii) 71-1441 or 152-1441 of (III);

(b) the nucleotide sequence (NS) of the full-length protein-coding sequence of clones dj1672, dj16719 and dw6654 (all clones are deposited as ATCC 98818 or ATCC 207090);

(c) a sequence encoding either the full-length or the mature protein encoded by the cDNA insert of the above clones;

(d) a sequence encoding a protein comprising one of the ten defined amino acid sequences (IV-(VI) (of 400, 1036 or 457 amino acids respectively) given in the specification or fragments comprising 8 consecutive amino acids;

(e) a PN that hybridizes under conditions at least as stringent as 4xSSC at 65 deg. C, or 4xSSC at 42 deg. C with 50% formamide, to any one of the PNs in (a)-(c);

(f) a PN that hybridizes under conditions at least as stringent as 4 x SSC at 50 deg. C, or 6 x SSC at 40 deg. C with 50% formamide, to any of the PNs in (a)-(c), and that has a length that is at least 25% of the length of sequences as in (a)-(c).

INDEPENDENT CLAIMS are also included for:
(1) proteins comprising:
(a) an amino acid sequence encoded by the cDNA insert of one of the above clones; or
(b) the 3 above-defined amino acid sequences (IV)-(VI) or fragments comprising 8 consecutive amino acids;
(c) an amino acid sequence comprising amino acids 637-1036 of (V);
(2) a PN as in (A) which is operably linked to at least one expression control sequence;
(3) a host cell transformed with (2); and
(4) a process for producing the above proteins encoding the above polynucleotides comprising:
(a) growing a culture of a host cell in a suitable culture medium where the host cell has been transformed with one of the above polynucleotides; and
(b) purifying the protein from the culture.
ACTIVITY - Vulnerary; Osteopathic; Antiulcer; Antiinflammatory; Neuroprotective.
Studies were carried out to demonstrate the extent of binding between an N-terminal fragment of the DW6654 protein (DW665-N) and different members of the bone morphogenetic protein (BMP) protein family to **detect** changes in surface plasmon resistance. The binding experiments indicate that the N-terminal fragment of the DW6654 protein has a Chordin-like protein-binding profile, and binds to BMP-2, BMP-4, **BMP-7** and GDF-5, and to a lesser degree to BMP-12 and BMP-13. However, this N-terminal fragment of DW6654 does not seem to inhibit BMP-2 in the W20 bioassay. This result suggests that the third Chordin cysteine repeat present in the DW665-C fragment may be necessary for BMP-inhibitory activity.
MECHANISM OF ACTION - Inducers of cartilage, bone or connective tissue formation.
USE - The PNs and proteins are predicted to have biological activities which would make them suitable for treating, preventing or ameliorating medical conditions selected from defects in cartilage, bone or connective **tissue** formation and damage to cartilage, bone or connective **tissue**, e.g. broken bones, congenital, trauma-induced, or oncologic-resection-induced craniofacial defects, periodontal **disease**, defects in the periodontal ligament or attachment apparatus, damage to the periodontal ligament or attachment apparatus, osteoporosis, burns, incisions or ulcers (claimed). It is further contemplated that the proteins may affect neuronal, astrocytic, and glial cell survival and therefore be useful in transplantation and treatment of conditions exhibiting a decrease in neuronal survival and repair. The proteins may further be useful for the treatment of conditions related to other types of **tissue**, such as nerve, epidermis, muscle, and other organs such as liver, brain, lung, cardiac, pancreas, and kidney **tissue**. The proteins may further be useful for the treatment of relatively undifferentiated cell populations, such as embryonic cells, or stem cells, to enhance growth and/or differentiation of the cells, such enhancement of growth and/or differentiation of these cells may particularly be carried out on isogenic or allogenic cells ex vivo, with subsequent reintroduction of the treatment cells to the patient. The proteins may also have other useful properties characteristic of the TGF- beta superfamily of proteins. Such properties include angiogenic, chemotactic, and/or chemoattractant properties, and effects on cells including induction or inhibition of collagen synthesis, fibrosis,

differentiation responses, cell proliferative responses, and responses involving cell adhesion, migration, and extracellular matrices. These properties make the proteins potential agents for wound healing, reduction of fibrosis, and reduction of scar **tissue** formation.
Chordin-related proteins may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs. It is further contemplated that chordin-related proteins may be useful in modulating hematopoiesis by inducing the differentiation of erythroid cells, for suppressing the development of gonadal tumors, or for augmenting the activity of BMPs. The proteins may also have value as a dietary supplement, or as a component of cell culture media.
Dwg.0/9

L11 ANSWER 23 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-531476 [48] WPIDS
CROSS REFERENCE: 1998-609325 [51]; 1999-130430 [11]
DOC. NO. NON-CPI: N2000-392919
DOC. NO. CPI: C2000-158398
TITLE: Identifying morphogen analogs useful for designing morphogen agonists and antagonists for therapeutic or **diagnostic** uses, comprises exposing a candidate morphogen analog to a morphogen receptor-1.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): JIN, D F; KUBERASAMPATH, T; OPPERMANN, H; SMART, J E
PATENT ASSIGNEE(S): (CREA-N) CREATIVE BIOMOLECULES INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6093547	A	20000725	(200048)*		31

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6093547	A	Cont of	US 1993-73199	19930607
		Div ex	US 1994-357533	19941216
			US 1995-459951	19950602

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6093547	A	Div ex	US 5831050

PRIORITY APPLN. INFO: US 1993-73199 19930607; US 1994-357533 19941216; US 1995-459951 19950602
AN 2000-531476 [48] WPIDS
CR 1998-609325 [51]; 1999-130430 [11]
AB US 6093547 A UPAB: 20001001
NOVELTY - Identifying a morphogen analog and predicting if it is capable of in vivo binding to a morphogen analog receptor comprises exposing it to a polypeptide (I) encoded by a DNA or its variant, where (I) is about 500

amino acids, has a molecular weight of 58 - 90 kDa, and has a binding specificity for **OP-1** or BMP-2, and does not substantially bind to transforming growth factor (TGF)- beta or activin.

DETAILED DESCRIPTION - Identifying a morphogen analog comprises selecting a candidate morphogen analog; exposing it to a composition containing (I) encoded by a DNA having a 2625 bp sequence, fully defined in the specification, or its variant, where (I) or its variant is about 500 amino acids, has a molecular weight of 58 - 90 kDa, and has a binding specificity for **OP-1** or BMP-2, and does not substantially bind to TGF- beta or activin; and **determining** whether the candidate morphogen analog binds to (I) or to its variant, where a candidate morphogen analog that binds to (I) is a morphogen analog.

INDEPENDENT CLAIMS are also included for the following:

(1) predicting whether a candidate morphogen analog is capable of in vivo binding to a morphogen receptor by employing the new method, where the morphogen analog that binds to (I) is predicted to be capable of in vivo binding to a morphogen receptor; and

(2) a kit for identifying a morphogen analog from a candidate morphogen analog comprising:

(a) a polypeptide having a ligand-binding domain of a morphogen receptor encoded by the DNA having a fully defined 2625 bp sequence given in the specification, or its allelic or species variant, where the polypeptide has a binding specificity for **OP-1** or BMP-2, while not substantially binding to TGF- beta or activin, is about 500 amino acids, and has a molecular weight of 58 - 90 kDa;

(b) a receptacle adapted to receive a sample comprising the candidate morphogen analog and the polypeptide of (a); and

(c) means for **detecting** specific binding interaction of the polypeptide with the candidate morphogen analog.

ACTIVITY - Vulnerary; osteopathic; cytostatic. No biological data is given.

MECHANISM OF ACTION - Gene therapy; morphogen agonist; morphogen antagonist. No biological data is given.

USE - The methods are useful for identifying morphogen analogs and morphogen receptors which may be used in therapeutic, **diagnostic** and experimental research applications as morphogen agonists or antagonists. Morphogen antagonists may be used to modulate uncontrolled differentiated **tissue** growth such as malignant transformations in osteosarcomas or Paget's **disease**, and as insecticides, which can interfere with insect growth and **tissue** development. Morphogen agonists are used where **tissue** morphogenesis is desired, e.g. in the regeneration of damaged **tissue** resulting from mechanical or chemical trauma, degenerative **diseases**, or **tissue** destruction.

Dwg.0/3

L11 ANSWER 24 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-422077 [36] WPIDS
CROSS REFERENCE: 1989-324202 [44]; 1989-324203 [44]; 1990-290311 [38]; 1991-148697 [20]; 1992-167101 [20]; 1992-167153 [20]; 1992-331475 [40]; 1993-100652 [12]; 1993-100993 [12]; 1993-117208 [14]; 1993-395405 [49]; 1994-007210 [01]; 1994-065304 [08]; 1994-065399 [08]; 1994-065689 [08]; 1994-118107 [14]; 1994-118121 [14]; 1994-118146 [14]; 1994-118148 [14]; 1994-167392 [20]; 1994-302971 [37];

1994-324521 [40]; 1996-010159 [01]; 1996-040236 [04];
1997-178399 [16]; 1997-384665 [35]; 1998-109345 [10];
1998-158353 [14]; 1998-260496 [23]; 1998-333785 [30];
1999-131303 [11]; 1999-589530 [50]; 2000-038265 [03];
2001-069971 [08]; 2002-415042 [44]; 2003-575998 [54];
2003-584258 [55]; 2003-801273 [75]; 2004-008898 [01];
2004-167144 [16]; 2004-374248 [35]

DOC. NO. CPI: C2000-127585

TITLE: **Screening** for compounds able to modulate **osteogenic protein-1** (**OP-1**) expression by incubating a candidate compound with a nucleic acid with a reporter gene operatively associated with an **OP-1** non-coding nucleic acid fragment.

DERWENT CLASS: B04 D16

INVENTOR(S): OPPERMANN, H; OZKAYNAK, E

PATENT ASSIGNEE(S): (CREA-N) CREATIVE BIOMOLECULES INC

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6071695	A	20000606	(200036)*		30

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6071695	A	Div ex	US 1992-841646	19920221
		Div ex	US 1993-147023	19931101
		CIP of	US 1994-255250	19940607
		CIP of	US 1995-449700	19950523
		CIP of	US 1995-449699	19950524
			US 1995-486343	19950607

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6071695	A	Div ex	US 5266683
		Div ex	US 5468845
		CIP of	US 5863758

PRIORITY APPLN. INFO: US 1995-486343 19950607; US 1992-841646 19920221; US 1993-147023 19931101; US 1994-255250 19940607; US 1995-449700 19950523; US 1995-449699 19950524

AN 2000-422077 [36] WPIDS

CR 1989-324202 [44]; 1989-324203 [44]; 1990-290311 [38]; 1991-148697 [20]; 1992-167101 [20]; 1992-167153 [20]; 1992-331475 [40]; 1993-100652 [12]; 1993-100993 [12]; 1993-117208 [14]; 1993-395405 [49]; 1994-007210 [01]; 1994-065304 [08]; 1994-065399 [08]; 1994-065689 [08]; 1994-118107 [14]; 1994-118121 [14]; 1994-118146 [14]; 1994-118148 [14]; 1994-167392 [20]; 1994-302971 [37]; 1994-324521 [40]; 1996-010159 [01]; 1996-040236 [04];

1997-178399 [16]; 1997-384665 [35]; 1998-109345 [10]; 1998-158353 [14]; 1998-260496 [23]; 1998-333785 [30]; 1999-131303 [11]; 1999-589530 [50]; 2000-038265 [03]; 2001-069971 [08]; 2002-415042 [44]; 2003-575998 [54]; 2003-584258 [55]; 2003-801273 [75]; 2004-008898 [01]; 2004-167144 [16]; 2004-374248 [35]

AB US 6071695 A UPAB: 20040603

NOVELTY - **Screening** a candidate compound for ability to modulate expression of **osteogenic protein-1** (**OP-1**) uses a cell transfected with a nucleic acid comprising a reporter gene and upstream non-coding sequence from **OP-1**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) an isolated nucleic acid (NA1) having a nucleotide sequence comprising nucleotides 1-3317 of a fully defined sequence (I) having 17415 base pair (bp) given in the specification;

(2) an isolated nucleic acid (NA2) having a nucleotide sequence comprising nucleotides 1-1871 of a fully defined sequence (II) having 1300 bp given in the specification;

(3) an isolated nucleic acid (NA3) comprising a reporter gene in operative association with a nucleic acid fragment of an **OP-1** protein specific upstream non-coding sequence, where the nucleic acid fragment consists of nucleotides 3170-3317, 3020-3317, 2790-3317-, 2548-3317, 2300-3317, 1300-3317, 2548-2790, 1549-2790, or 1-2790 of (I);

(4) a cell transfected with NA3;

(5) an isolated nucleic acid (NA4) comprising a reporter gene in operative association with:

(a) a nucleic acid fragment of an **OP-1** specific upstream non-coding sequence, where the fragment consists of nucleotides 2151-2297, 2001-2297, 1788-2297, 1549-2297, 800-2297, 1-2297, 1549-1788, 800-1788, or 1-1788 of (II); or

(b) a variant of (5a) which hybridizes with a nucleic acid complementary to (5a) under conditions of hybridization in 40% formamide, 5 multiply SSPE, 5 multiply Denhardt's solution, and 0.1% sodium dodecyl sulfate (SDS) at 37 deg. C, followed by washing in 0.1 multiply SSPE, and 0.1% SDS at 50 deg. C, where (5a) or (5b) is operative to regulate reporter gene expression;

(6) a method of **screening** a candidate compound for the ability to modulate expression of **osteogenic protein-1** (**OP-1**) comprises incubating a candidate compound with a cell transfected with NA3 or NA4, **measuring** reporter gene expression level in the cell, and comparing this level with the gene expression level in a cell without the candidate compound, where an increase in reporter gene expression level is an indication of the compounds ability to increase **OP-1** expression in vivo;

(7) kits for identifying a candidate molecule capable of modulating **OP-1** expression in a cell comprising a receptacle containing a NA3 or NA4 and a device for **detecting** expression of the reporter gene following exposure of the candidate molecule to a cell containing the nucleic acid;

(8) a vector comprising NA1, NA3 or NA4; and

(9) a cell transfected with an isolated nucleic acid, which comprise a reporter gene in operative association with a first DNA sequence, the first DNA sequence is:

(a) single nucleic acid fragment or an **OP-1** specific upstream non-coding sequence, where the nucleic acid fragment

consists of nucleotides 2548-3317 or 2548-2790 of (I);
(b) a nucleic acid fragment of an **OP-1** specific upstream non-coding sequence, where nucleic acid fragment consists of nucleotides 1549-2297 or 1549-1788 of (II); or
(c) a variant of (9b) which hybridizes with a nucleic acid complementary to (9b) under hybridization conditions in 40% formamide, 5 multiply SSPE, 5 multiply Denhardt's solution, and 0.1% SDS at 37 deg. C, followed by washing in 0.1 multiply SSPE, and 0.1% SDS at 50 deg. C, where (9a) or (9b) is operative to regulate reporter gene expression; and a second DNA sequence comprising a sequence which interacts with a DNA binding molecule and affects expression of the reporter gene, where the isolated nucleic acid comprises not more than one nucleic acid fragment of (9a).
USE - The method is useful for **screening** compounds capable of stimulating or inhibiting transcription and/or translation of the **OP-1** gene, as well as compounds which may be used as therapeutics for in vivo and ex vivo mammalian applications, e.g. morphogen expression inducing compounds for correcting and alleviating a **diseased** condition or to regenerate lost or damaged **tissue** . The compounds may also be used to maintain viability of the differentiated phenotype of cells in culture. Morphogen expression inhibiting compounds identified by the new method can be used to modulate the degree and/or timing of morphogen. Compounds which up-regulate levels of circulating **OP-1** in vivo can be used to correct bone metabolism **diseases** such as osteoporosis.
Dwg.0/5

L11 ANSWER 25 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-385570 [32] WPIDS
DOC. NO. CPI: C1999-113476
TITLE: New Purified bone morphogenic protein-17 and -18 (BMP-17 and BMP-18) polypeptides, useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells.
DERWENT CLASS: B04 D16
INVENTOR(S): CELESTE, A J; MURRAY, B L
PATENT ASSIGNEE(S): (GEMY) GENETICS INST INC; (CELE-I) CELESTE A J; (MURR-I) MURRAY B L; (GEMY) GENETICS INST LLC
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9929718	A2	19990617	(199932)*	EN	39
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
AU 9914631	A	19990628	(199946)		
US 6027917	A	20000222	(200017)		
EP 1037907	A2	20000927	(200048)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2002505851	W	20020226	(200219)		60
MX 2000005709	A1	20010701	(200236)		

US 2002143159 A1 20021003 (200267)
US 6492493 B2 20021210 (200301)
AU 763470 B 20030724 (200355)
US 2003149241 A1 20030807 (200358)
EP 1420031 A2 20040519 (200433) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9929718	A2	WO 1998-US24613	19981117
AU 9914631	A	AU 1999-14631	19981117
US 6027917	A	US 1997-987904	19971210
EP 1037907	A2	EP 1998-958631	19981117
		WO 1998-US24613	19981117
JP 2002505851	W	WO 1998-US24613	19981117
		JP 2000-524309	19981117
MX 2000005709	A1	MX 2000-5709	20000609
US 2002143159	A1 Div ex	US 1997-987904	19971210
		US 1999-438623	19991112
US 6492493	B2 Div ex	US 1997-987904	19971210
		US 1999-438623	19991112
AU 763470	B	AU 1999-14631	19981117
US 2003149241	A1 Div ex	US 1997-987904	19971210
	Cont of	US 1999-438623	19991112
		US 2002-228808	20020826
EP 1420031	A2 Div ex	EP 1998-958631	19981117
		EP 2003-28954	19981117

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9914631	A Based on	WO 9929718
EP 1037907	A2 Based on	WO 9929718
JP 2002505851	W Based on	WO 9929718
US 6492493	B2 Div ex	US 6027917
AU 763470	B Previous Publ.	AU 9914631
	Based on	WO 9929718
US 2003149241	A1 Div ex	US 6027917
EP 1420031	A2 Div ex	EP 1037907

PRIORITY APPLN. INFO: US 1997-987904 19971210; US 1999-438623 19991112; US 2002-228808 20020826

AN 1999-385570 [32] WPIDS
AB WO 9929718 A UPAB: 19990813
NOVELTY - Purified bone morphogenic protein (BMP) polypeptides (I), comprising amino acids 1-224 (BMP-17) or amino acids 1-231 (BMP-18) from fully defined 366 amino acid proteins given in the specification.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) an isolated DNA molecule (II) comprising a DNA sequence selected from:
(a) nucleotides 1, 232, 406, 427, 751 or 796 to 1059 or 1098 of fully

defined 1101 cDNA sequences given in the specification;
(b) nucleotides encoding amino acids -142, -65, -7, 1, 109 or 124 to 211 or 224 of BMP-17;
(c) nucleotides encoding amino acids -135, -58, 1, 8, 116 or 131 to 218 or 231 of BMP-18; and
(d) naturally occurring human allelic sequences and equivalent degenerative codon sequences of (a)-(c);
(2) a host cell transformed with (II);
(3) a vector comprising (II) in operative association with an expression control sequence;
(4) a host cell transformed with (3);
(5) preparation of (I);
(6) a chimeric DNA molecule comprising a DNA sequence encoding a propeptide from a member of the TGF- beta superfamily of proteins linked in frame to a DNA sequence encoding BMP-17 or BMP-18 comprising amino acids 1-224 of the 366 sequence given in the specification; and
(7) antibodies to BMP-17 and BMP-18.
ACTIVITY - BMP-17 and BMP-18 stimulate FSH.
USE - (I) is useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells, and for the treatment of bone, cartilage and other connective **tissue** defects including tendons, ligaments and meniscus, in wound healing and related **tissue** repair, and for treatment of **disorders** and defects to **tissues** which include epidermis, nerve, muscle, including cardiac muscle, and other **tissues** and wounds, and organs such as liver, lung, epithelium, brain, spleen, cardiac, pancreas and kidney **tissue**.
DNA (II) is useful as probes to **detect** expression of (I), and the vectors are useful for delivery of (I) to cells of a patient.
Dwg.0/0

L11 ANSWER 26 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER:	2000-038265 [03] WPIDS
CROSS REFERENCE:	1989-324202 [44]; 1989-324203 [44]; 1990-290311 [38]; 1991-148697 [20]; 1992-167101 [20]; 1992-167153 [20]; 1992-331475 [40]; 1993-100652 [12]; 1993-100993 [12]; 1993-117208 [14]; 1993-395405 [49]; 1994-007210 [01]; 1994-065304 [08]; 1994-065399 [08]; 1994-065689 [08]; 1994-118107 [14]; 1994-118121 [14]; 1994-118146 [14]; 1994-118148 [14]; 1994-167392 [20]; 1994-302971 [37]; 1994-324521 [40]; 1996-010159 [01]; 1997-178399 [16]; 1997-384665 [35]; 1998-109345 [10]; 1998-158353 [14]; 1998-260496 [23]; 1998-333785 [30]; 1999-131303 [11]; 1999-589530 [50]; 2000-422077 [36]; 2001-069971 [08]; 2002-415042 [44]; 2003-575998 [54]; 2003-584258 [55]; 2003-801273 [75]; 2004-008898 [01]; 2004-167144 [16]; 2004-374248 [35]
DOC. NO. CPI:	C2000-009710
TITLE:	**Screening** assay useful for identifying compounds which can act to modulate expression of a morphogen in a mammalian cell.
DERWENT CLASS:	B04 D16
INVENTOR(S):	COHEN, C M; KUBERASAMPATH, T; OPPERMANN, H; OZKAYNAK, E; PANG, R H L; RUEGER, D C; SMART, J E
PATENT ASSIGNEE(S):	(CREA-N) CREATIVE BIOMOLECULES INC
COUNTRY COUNT:	1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5994131	A	19991130	(200003)*		48

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5994131	A	CIP of	US 1991-667274	19910311
		CIP of	US 1991-752764	19910830
		CIP of	US 1991-752861	19910830
		Cont of	US 1992-938021	19920828
		Cont of	US 1994-278729	19940720
		Div ex	US 1995-451953	19950526
			US 1997-912088	19970815

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5994131	A	Cont of	US 5650276
		Div ex	US 5741641

PRIORITY APPLN. INFO: US 1992-938021 19920828; US 1991-667274 19910311; US 1991-752764 19910830; US 1991-752861 19910830; US 1994-278729 19940720; US 1995-451953 19950526; US 1997-912088 19970815

AN 2000-038265 [03] WPIDS

CR 1989-324202 [44]; 1989-324203 [44]; 1990-290311 [38]; 1991-148697 [20]; 1992-167101 [20]; 1992-167153 [20]; 1992-331475 [40]; 1993-100652 [12]; 1993-100993 [12]; 1993-117208 [14]; 1993-395405 [49]; 1994-007210 [01]; 1994-065304 [08]; 1994-065399 [08]; 1994-065689 [08]; 1994-118107 [14]; 1994-118121 [14]; 1994-118146 [14]; 1994-118148 [14]; 1994-167392 [20]; 1994-302971 [37]; 1994-324521 [40]; 1996-010159 [01]; 1997-178399 [16]; 1997-384665 [35]; 1998-109345 [10]; 1998-158353 [14]; 1998-260496 [23]; 1998-333785 [30]; 1999-131303 [11]; 1999-589530 [50]; 2000-422077 [36]; 2001-069971 [08]; 2002-415042 [44]; 2003-575998 [54]; 2003-584258 [55]; 2003-801273 [75]; 2004-008898 [01]; 2004-167144 [16]; 2004-374248 [35]

AB US 5994131 A UPAB: 20040603

NOVELTY - Altering expression of a morphogen in a mammalian cell with a compound identified by a **screening** assay is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a method for altering the expression of a morphogen in a mammalian cell comprising:

(1) providing a compound that modulates morphogen expression in epithelial cells identified in an assay for bone formation which comprises:

(i) incubating the compound with epithelial cells expressing a protein which induces endochondral bone formation in an in vivo assay comprising:

(a) a polypeptide with at least 70% amino acid (aa) sequence homology with the C-terminal seven cysteine domain of human **OP-1**

, a morphogenic protein which is a member of the transforming growth factor (TGF- beta) superfamily, (residues 38-139 of the human **OP -1** mature protein sequence which is 139 aa long and given in the specification);

(b) a polypeptide defined by Generic Sequence 6, a protein sequence of 102 aa given in the specification which provides an appropriate cysteine skeleton where inter- or intramolecular disulfide bonds can form containing certain critical aa influencing the tertiary structure of the protein; or

(c) a polypeptide selected from a group of native proteins identified as morphogens given in the specification e.g. human and mouse **OP -1** and OP-2;

(ii) **measuring** a test amount of the protein expressed in the epithelial cells in the presence of the compound; and

(iii) comparing the test amount to a constitutive amount of the protein expressed in the epithelial cells in the absence of the compound where a difference indicates that the compound modulates morphogen expression in epithelial cells; and

(2) contacting a mammalian cell with the compound to alter morphogen expression in the mammalian cell.

USE - The method is used as a **screening** assay for identifying compounds which modulate the level of expression of a morphogen. The method allows the **determination** of substances useful in therapeutic treatments to modulate (stimulate or depress) morphogen expression and/or secretion in **disease** treatment. Compounds can be **screened** for their ability to modulate the effective systemic or local concentration of a morphogen. Compounds which can be **screened** include chemicals, biological response molecules such as lymphokines, cytokines, hormones or vitamins, plant extracts, microbial broths and extract mediums conditioned by eukaryotic cells, body fluids or **tissue** extracts.

ADVANTAGE - The assay has few steps and is easy to carry out producing results quickly. Drugs which result in cell death are easy to identify

Dwg.0/3

L11 ANSWER 27 OF 41 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2000:108050 BIOSIS
DOCUMENT NUMBER: PREV200000108050
TITLE: **OP-1** for cervical spine fusion: Bridging bone in only 1 of 4 rheumatoid patients but prednisolone did not inhibit bone induction in rats.
AUTHOR(S): Jeppsson, Charlotte [Reprint author]; Saveland, Hans; Rydholm, Urban [Reprint author]; Aspenberg, Per [Reprint author]
CORPORATE SOURCE: Department of Orthopedics, Lund University Hospital, SE-221 85, Lund, Sweden
SOURCE: Acta Orthopaedica Scandinavica, (Dec., 1999) Vol. 70, No. 6, pp. 559-563. print.
CODEN: AOSAAK. ISSN: 0001-6470.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Mar 2000
Last Updated on STN: 3 Jan 2002

AB We used **OP-1** (also called **BMP-7**)

on a collagen type-1 carrier in atlanto-axial posterior fusions to promote bony healing after wire fixation. 4 patients who had instability between the atlas and axis due to rheumatoid disease received the implants. The patients were examined with conventional radiography postoperatively at 2, 6 and 10 months. In 3 patients, no new bone formation was **detectable**. In 1 patient, new bone bridged the fusion site at 6 months. 3 patients were on chronic steroid treatment, including the patient in whom bone formation was **detected**. To **determine** whether steroid treatment could be responsible for the low rate of bone induction, 24 rats each received **OP-1** implants in an abdominal muscle pouch. They were divided into 3 groups receiving saline, 0.1 or 1.0 mg/kg BW of prednisolone daily until they were killed 3 weeks postoperatively. Specimens were decalcified for histology and the amount of calcium in the decalcifying solution was **measured**. All groups showed ossicles induced by **OP-1**, and no effect of prednisolone was **detected**. Thus the failures in the patients may have causes other than prednisolone treatment.

L11 ANSWER 28 OF 41 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 5

ACCESSION NUMBER: 1999340804 EMBASE
TITLE: Role of polypeptides in the treatment and **diagnosis** of osteoporosis.
AUTHOR: Kundu B.; Khare S.K.; Singh G.
CORPORATE SOURCE: B. Kundu, Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226001, India. root@cscdri.ren.nic.in
SOURCE: Peptides, (1999) 20/4 (523-537).
Refs: 165
ISSN: 0196-9781 CODEN: PEPTDO
PUBLISHER IDENT.: S 0196-9781(99)00034-0
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
003 Endocrinology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Osteoporosis is a common **disorder** characterized by reduced bone mineral density, deterioration of the microarchitecture of bone **tissue** and increased risk of fracture. The aim of treatment of osteoporosis is to maintain and, ideally, to restore bone strength safely. In recent years the role of polypeptide growth factors in bone metabolism has begun to appear. It has been proposed that alterations in the expression or production of growth factor can modulate the proliferation and activity of bone forming cells. In this direction, the role of structurally diverse peptides for the management and **diagnosis** of osteoporosis has attracted the attention of many investigators. This paper reviews numerous findings concerning the use of polypeptides, hormones, and growth factors, for the management of osteoporosis. Many of the compounds mentioned here are experimental prototypes of new therapeutic classes. Though it is unlikely that some of the compounds may ever be used clinically, development of safe and efficacious agents in each class will define the future course of therapy for osteoporosis.

L11 ANSWER 29 OF 41 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000070545 EMBASE
TITLE: Lineage-restricted expression of bone morphogenetic protein genes in human hematopoietic cell lines.
AUTHOR: Detmer K.; Steele T.A.; Shoop M.A.; Dannawi H.
CORPORATE SOURCE: Dr. K. Detmer, Division of Basic Medical Sciences, Mercer University School of Medicine, 1550 College St., Macon, GA 31207, United States. detmer.k@gain.mercer.edu
SOURCE: Blood Cells, Molecules, and Diseases, (1999) 25/5-6 (310-323).
Refs: 55
ISSN: 1079-9796 CODEN: BCMDFX
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB To explore the possibility that bone morphogenetic proteins (BMPs) are autocrine/paracrine regulators of hematopoietic differentiation and function, we **screened** a panel of human cell lines encompassing the hematopoietic lineages for expression of members of this family of genes. Expression of BMP-2, BMP-4, BMP-6, **BMP-7**, Growth and Differentiation Factor-1 (GDF-1), Placental Bone Morphogenetic Protein (PLAB), and Transforming Growth Factor- β3 (TGF-β3) was **detected** in one or more cell lines. BMP-2, BMP-4, **BMP-7**, and TGF-β3 expression was also found in normal hematopoietic **tissue**. Expression of BMP-5 and BMP-8 was not seen. Lineage-restricted patterns of expression were found for BMP-4 (T-lymphoid), **BMP-7** (lymphoid), PLAB (macrophage/monocyte), and GDF-1 (myeloid). Expression of BMP-2, GDF-1, and PLAB could be modulated by treatment with differentiating agents. Marked variations in the levels of BMP-4, **BMP-7**, and PLAB expression were encountered, indicating that **disorders** in BMP signaling pathways may play a role in the development of hematopoietic neoplasia. (C) 1999 Academic Press.

L11 ANSWER 30 OF 41 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1999:939414 SCISEARCH
THE GENUINE ARTICLE: 260PF
TITLE: Lineage-restricted expression of bone morphogenetic protein genes in human hematopoietic cell lines
AUTHOR: Detmer K (Reprint); Steele T A; Shoop M A; Dannawi H
CORPORATE SOURCE: MERCER UNIV, SCH MED, DIV BASIC MED SCI, 1550 COLL ST, MACON, GA 31207 (Reprint); MED CTR CENT GEORGIA, DEPT PEDIAT, MACON, GA
COUNTRY OF AUTHOR: USA
SOURCE: BLOOD CELLS MOLECULES AND DISEASES, (15 NOV 1999) Vol. 25, No. 21, pp. 310-323.
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 1079-9796.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 55

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB To explore the possibility that bone morphogenetic proteins (BMPs) are autocrine/paracrine regulators of hematopoietic differentiation and function, we **screened** a panel of human cell lines encompassing the hematopoietic lineages for expression of members of this family of genes. Expression of BMP-2, BMP-4, BMP-6, **BMP-7**, Growth and Differentiation Factor-1 (GDF-1), Placental Bone Morphogenetic Protein (PLAB), and Transforming Growth Factor-beta 3 (TGF-beta 3) was **detected** in one or more cell lines. BMP-2, BMP-1, **BMP-7**, and TGF-beta 3 expression was also found in normal hemaropoietic **tissue**. Expression of BMP-5 and BMP-S was not seen. Lineage-restricted patterns of expression were found for BMP-4 (T-lymphoid), **BMP-7** (lymphoid), PLAB (macrophage/monocyte), and GDF-1 (myeloid), Expression of BMP-2, CDF-1, and PLAB could be modulated by treatment with differentiating agents. Marked variations in the levels of BMP-4, **BMP-7**, and PLAB expression were encountered, indicating that **disorders** in BMP signaling pathways may play a role in the development of hematopoietic neoplasia.

L11 ANSWER 31 OF 41 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 6

ACCESSION NUMBER: 2002:89857 BIOSIS
DOCUMENT NUMBER: PREV200200089857
TITLE: Method of **diagnosing** renal **tissue** damage or **disease**.
AUTHOR(S): Smart, J. E. [Inventor]; Oppermann, H. [Inventor]; Ozkaynak, E. [Inventor]; Kuberasampath, T. [Inventor]; Rueger, D. C. [Inventor]; Pang, R. H. L. [Inventor]; Cohen, C. M. [Inventor]
CORPORATE SOURCE: Weston, Mass., USA
ASSIGNEE: CREATIVE BIOMOLECULES, INC.
PATENT INFORMATION: US 5707810 Jan. 13, 1998
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Jan. 13, 1998) Vol. 1206, No. 2, pp. 1342. print.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jan 2002
Last Updated on STN: 25 Feb 2002

L11 ANSWER 32 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-348526 [30] WPIDS
DOC. NO. CPI: C1998-107827
TITLE: Identifying morphogen analogues - by using DNA defining a morphogen-responsive transcription activating element from a mouse type X collagen promoter.
DERWENT CLASS: B04 D16
INVENTOR(S): HARADA, S; RODAN, G A; SAMPATH, K T
PATENT ASSIGNEE(S): (CREA-N) CREATIVE BIOMOLECULES INC
COUNTRY COUNT: 21

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9826069	A1	19980618	(199830)*	EN	88
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9858988	A	19980703	(199847)		
US 6090544	A	20000718	(200037)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9826069	A1	WO 1997-US23211	19971211
AU 9858988	A	AU 1998-58988	19971211
US 6090544	A CIP of	US 1995-507598	19950726
		US 1996-764522	19961212

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9858988	A Based on	WO 9826069

PRIORITY APPLN. INFO: US 1996-764522 19961212; US 1995-507598 19950726

AN 1998-348526 [30] WPIDS

AB WO 9826069 A UPAB: 19980730

The following are claimed: (A) identification of a compound that induces a morphogen-mediated biological effect, comprising: (a) providing a test cell comprising DNA defining a morphogen-responsive transcription activating element (MRTAE), and, in operative association, a reporter gene encoding a **detectable** gene product, the DNA, when present in a morphogen-responsive cell contacted with morphogen, serving to induce transcription of the reporter gene; (b) exposing the test cell to a candidate compound, and (c) **detecting** expression of the **detectable** gene product, the expression indicating the ability of the candidate compound to induce the morphogen-mediated biological effect; (B) a method of assessing whether a sample comprises a substance competent to bind to DNA, the sequence of which comprises nucleotides 699-731 of a sequence shown, comprising: (a) providing DNA, the sequence of which comprises nucleotides 699-731 of a sequence shown; (b) exposing the DNA to the sample; and (c) **detecting** the binding of the substance to the DNA; (C) a pure substance competent to bind to DNA, the sequence of which comprises nucleotides 699-731 of a sequence shown, such that the substance has the property of modulating expression of a gene encoding a gene product when the DNA is in operative association with it and the substance is bound to it; (D) an isolated DNA sequence defining a MRTAE comprising: (a) nucleotides 699-731, 682-731, or 682-761 of a sequence shown; (b) species and allelic variants of (a); (c) DNA which hybridises to the strand complementary to sequence (a) and is morphogen-responsive under native conditions; and (d) biosynthetic variants of any of (a), (b) and (c); (E) an isolated polypeptide chain comprising: (a) a morphogen-inducible DNA binding protein which can interact with nucleotides 699-711, 715-724, 699-731, 682-731, 703-724, or 682-761 of a

sequence shown; (b) species or allelic variants of (a); (c) truncated amino acid sequences of any of (a) and (b) inducible by a morphogen or analogue under native conditions; (d) biosynthetic or recombinant variants of any of the above; (F) an isolated binding protein having binding specificity for a polypeptide chain as in (E); (G) a cell transfected with any one of the DNA sequences as in (D); (H) a method for identifying a candidate compound that induces a morphogen-mediated biological effect comprising: (a) providing a test cell comprising DNA defining a MRTAE, the DNA, when present in a morphogen responsive cell contacted with morphogen, serving to induce transcription of a reporter gene operatively associated with the transcription activating element (TAE); (b) exposing the test cell to a candidate compound; and (c) **detecting** morphogen inducible DNA binding to the TAE by a cellular protein, the binding indicating the ability of the candidate compound to induce the morphogen mediated biological effect; where step (c) occurs within 2-12 hours of completing step (b); (I) a method for monitoring cell differentiation or tissue morphogenesis comprising **detecting** DNA binding of a protein as in (E) in a cell exposed to a morphogen or analogue, and (J) a method for identifying a tissue responsive to a morphogen or analogue comprising **detecting** DNA binding of a protein as in (E) in the tissue, or a cell, exposed to the morphogen or analogue.

USE - The methods can be used for obtaining morphogen analogues. In particular they can be used for obtaining analogues of **osteogenic protein 1** (**OP-1**) for the treatment of a metabolic bone **disease**, e.g. a **disease** characterised by osteopenia. Analogues can also be obtained for treating mammals afflicted with ischemic, ulcerative or inflammatory **tissue** damage, or with injury or deterioration of a morphogen-responsive **tissue** such as bone, liver, kidney, nerve, gastrointestinal tract lining, tooth dentin or periodontal **tissue**.

Dwg.0/12

L11 ANSWER 33 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-230715 [20] WPIDS
DOC. NO. CPI: C1998-072207
TITLE: New isolated morphogen-responsive signal transducer, DD-10 - useful for, e.g. developing products for **tissue** regeneration or for treating **tissue** destruction or degenerative **disease**(s).
DERWENT CLASS: B04 D16
INVENTOR(S): ICHIJO, H; SAMPATH, K T; TAKEDA, K
PATENT ASSIGNEE(S): (CURI-N) CURIS INC; (CREA-N) CREATIVE BIOMOLECULES INC
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9813509	A1	19980402	(199820)*	EN	86
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9744999	A	19980417	(199834)		
US 5928940	A	19990727	(199936)		
EP 950110	A1	19991020	(199948)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2001501096	W	20010130	(200110)		97

AU 743744 B 20020207 (200224)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9813509	A1		WO 1997-US17144	19970924
AU 9744999	A		AU 1997-44999	19970924
US 5928940	A	Provisional	US 1996-25311P	19960924
			US 1996-727118	19961008
EP 950110	A1		EP 1997-943550	19970924
			WO 1997-US17144	19970924
JP 2001501096	W		WO 1997-US17144	19970924
			JP 1998-515872	19970924
AU 743744	B		AU 1997-44999	19970924

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9744999	A	Based on	WO 9813509
EP 950110	A1	Based on	WO 9813509
JP 2001501096	W	Based on	WO 9813509
AU 743744	B	Previous Publ.	AU 9744999
		Based on	WO 9813509

PRIORITY APPLN. INFO: US 1996-727118 19961008; US 1996-25311P 19960924

AN 1998-230715 [20] WPIDS

AB WO 9813509 A UPAB: 19980520

The following are claimed: (1) An isolated DNA sequence defining a gene comprising: (a) nt residues 905-1264 of a 3611 bp sequence (I) (given in the specification); (b) species and allelic variants of (a); (c) DNA hybridising to a strand complimentary to sequence (a) and inducible by **osteogenic protein-1** (**OP1**), and (d) biosynthetic variants of any of (a)-(c); (2) a sequence similar to (1), comprising: (a) nt residues 121-780, 600-900, or 1-904 of (I), and (b) as in (1a)-(1c); (3) a sequence similar to (1), comprising: (a) nt residues 1-1264 or 1-3611 of (I), and (b) as in (2b); (4) an isolated polypeptide chain comprising: (a) aa residues 1-120 of a 120 aa sequence (II) (given in the specification); (b) as in (1a); (c) aa sequence encoded by a gene represented by a sequence (I); (d) truncated aa sequences of any of (a) and (b) and inducible by **OP-1**, and (e) biosynthetic or recombinant variants of any of the above; (5) an isolated binding protein (BP) having binding specificity for a polypeptide chain comprising a sequence (II); (6) an isolated antisense DNA corresponding to any of (1)-(3); (7) a vector comprising any one of the DNA sequences (1)-(3); (8) a cell transfected with a vector of (7); (9) a kit comprising: (a) a receptacle for containing a morphogen responsive test cell, and (b) a test cell comprising a DD-10 DNA sequence; (10) a method for identifying a candidate compound that induces an **OP1**-mediated biological effect comprising: (a) providing a test cell comprising DNA encoding an **OP1** responsive signal transducer element, where the DNA present in an **OP1** responsive cell contacted with **OP1** is induced to express a **detectable** expression product; (b) exposing the test cell to a candidate compound, and (c) **detecting** the

detectable expression product, where the expression indicates the ability of the candidate compound to induce the **OP1** mediated biological effect and where step (c) occurs within approx. 2-10 hours of completing step (b), and (11) a cell transfected with the DNA of (7).

USE - The gene designated DD-10 is expressed during early onset of morphogen-induced mammalian **tissue** morphogenesis. It can be used as a marker of cell differentiation and **tissue** morphogenesis (especially chondroblast or osteoblast cell differentiation) and bone **tissue** morphogenesis (claimed). The products can be used for identifying agents which induce or inhibit a morphogen-mediated biological effect (claimed). The agonists can be used for the treatment of **disease**, injuries and deteriorative **disorders**, especially those related to disruptions and/or abnormalities of developmental and metabolic pathways involved in **tissue** morphogenesis and **tissue** repair. They can be used for the regeneration of damaged **tissue** resulting from mechanical or chemical trauma, degenerative **diseases**, **tissue** destruction resulting from chronic inflammation, cirrhosis, inflammatory **diseases**, or cancer and in the regeneration of **tissues**, organs and limbs. The antagonists can be used for the killing or inhibition of the growth of target cells, e.g. in the treatment of malignant transformations including osteosarcomas, Paget's **disease** or fibrodysplasia ossificans progressiva. The products can also be used for **detection** and **diagnosis**.

Dwg.0/12

L11 ANSWER 34 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-165245 [15] WPIDS
DOC. NO. CPI: C1997-053295
TITLE: Analogue of **osteogenic protein-1**, receptor complex and binding partner - used to inhibit effects of **OP-1** on responsive cells, e.g. to treat osteo sarcoma and Paget's disease.
DERWENT CLASS: B04 D16
INVENTOR(S): ICHIJO, H; NISHITOH, H; SAMPATH, K T
PATENT ASSIGNEE(S): (CREA-N) CREATIVE BIOMOLECULES INC; (LUDW-N) LUDWIG INST CANCER RES; (CURI-N) CURIS INC
COUNTRY COUNT: 73
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9707135	A2	19970227	(199715)*	EN	64
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN					
AU 9667741	A	19970312	(199727)		
WO 9707135	A3	19970522	(199737)		
EP 845006	A2	19980603	(199826)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
AU 709991	B	19990909	(199949)		
US 5968752	A	19991019	(199950)		
JP 2000514777	W	20001107	(200059)		80

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9707135	A2		WO 1996-US13163	19960813
AU 9667741	A		AU 1996-67741	19960813
WO 9707135	A3		WO 1996-US13163	19960813
EP 845006	A2		EP 1996-928166	19960813
			WO 1996-US13163	19960813
AU 709991	B		AU 1996-67741	19960813
US 5968752	A	Provisional	US 1995-2313P	19950814
			US 1996-696268	19960813
JP 2000514777	W		WO 1996-US13163	19960813
			JP 1997-509445	19960813

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9667741	A	Based on	WO 9707135
EP 845006	A2	Based on	WO 9707135
AU 709991	B	Previous Publ.	AU 9667741
		Based on	WO 9707135
JP 2000514777	W	Based on	WO 9707135

PRIORITY APPLN. INFO: US 1995-2313P 19950814; US 1996-696268 19960813

AN 1997-165245 [15] WPIDS

AB WO 9707135 A UPAB: 20040102

A new isolated analogue (A) of osteogenic protein (**OP**)-**1** has the following characteristics: (i) binds to the ligand binding domain (LBD) of a cell surface receptor designated ALK-1 (503 amino acids (aa) given in the specification) or its variants; and (ii) has over 60% homology with the C-terminal 96 aa of **OP-1** (sequence given in the specification).

USE - (A) is applied to an **OP-1** responsive cell to antagonise either binding of **OP-1** or induction of **OP-1** mediated cell responses. Typical uses are to inhibit uncontrolled growth of differentiated **tissue**, e.g. in osteosarcoma or Paget's **disease**. The disclosure also contemplates that some (A) are **OP-1** agonists. A similar effect on **OP-1** responsive cells is achieved with soluble forms of ALK-1, or its **OP-1** specific analogues, and provided (A) is at least 60% homologous with the 335-431 region of **OP-1** it will also antagonise binding of activin and bone morphogenic protein (BMP)-4 to surface receptors. Other uses of (A) are (i) affinity purification and **quantitation** of **OP-1** and analogues (e.g. for **diagnosis** of osteoporosis, aplastic bone **disease** or osteopaenia); (ii) **determn./quantitation** of ALK-1. ALK-1 can be used to **screen** for ligands that modulate endogenous morphogen receptor expression levels. Chimeric forms of ALK-1 (having domains from other receptors or cell surface molecules) c an be used similarly and also in gene therapy, in combination with a specific morphogen agonist, to stimulate proliferation and differentiation of implanted, but not endogenous, cells. Nucleic acid probes based on the ALK-1 sequence can be

used to identify other **OP-1** specific receptors and their **tissue** distribution.
Dwg.0/2

L11 ANSWER 35 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-145719 [13] WPIDS
DOC. NO. CPI: C1997-046630
TITLE: **Screening** for morphogen analogues - using cells comprising a morphogen-responsive transcription activating element operatively linked to a reporter gene.
DERWENT CLASS: B04 D16
INVENTOR(S): HARADA, S; RODAN, G A; SAMPATH, K T
PATENT ASSIGNEE(S): (CREA-N) CREATIVE BIOMOLECULES INC
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9705285	A2	19970213	(199713)*	EN	61
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP					
AU 9666490	A	19970226	(199725)		
WO 9705285	A3	19970306	(199728)		
EP 840801	A2	19980513	(199823)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 5834188	A	19981110	(199901)		
JP 11510387	W	19990914	(199948)		70
AU 716578	B	20000302	(200021)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9705285	A2	WO 1996-US12078	19960722
AU 9666490	A	AU 1996-66490	19960722
WO 9705285	A3	WO 1996-US12078	19960722
EP 840801	A2	EP 1996-926105	19960722
		WO 1996-US12078	19960722
US 5834188	A	US 1995-507598	19950726
JP 11510387	W	WO 1996-US12078	19960722
		JP 1997-507674	19960722
AU 716578	B	AU 1996-66490	19960722

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9666490	A	Based on	WO 9705285
EP 840801	A2	Based on	WO 9705285
JP 11510387	W	Based on	WO 9705285
AU 716578	B	Previous Publ.	AU 9666490
		Based on	WO 9705285

PRIORITY APPLN. INFO: US 1995-507598 19950726
AN 1997-145719 [13] WPIDS
AB WO 9705285 A UPAB: 19970326

A novel method for identifying a cpd. that induces an **osteogenic protein-1** (**OP-1**) -mediated biological effect, comprises: (a) providing a test cell comprising DNA encoding an **OP-1** responsive transcription activating element (TAE), operatively linked to a reporter gene encoding a **detectable** gene prod., the DNA, when present in an **OP-1** responsive cell contacted with **OP-1**, serving to induce transcription of the reporter gene; (b) exposing the test cell to a candidate cpd; and (c) **detecting** expression of the **detectable** gene prod., which indicates the ability of the candidate cpd. to induce the **OP-1** mediated biological effect.

USE - The prods. and methods are used for identifying agents which can induce a morphogen-mediated biological effect, e.g. for the treatment of metabolic bone **disease** such as osteopenia or ischemic, ulcerative or inflammatory **tissue** damage or with injury or deterioration of a morphogen-responsive **tissue** such as bone, liver, nerve, gastrointestinal tract lining, tooth dentin or periodontal **tissue**. Such agents can also be used for the treatment or preservation of mammalian **tissue** or cells, eg. for organ or **tissue** transplantation.

Dwg.0/12

L11 ANSWER 36 OF 41 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1998:187783 SCISEARCH
THE GENUINE ARTICLE: YZ510
TITLE: Orthotopic ossification of the spinal ligaments of Zucker fatty rats: A possible animal model for ossification of the human posterior longitudinal ligament
AUTHOR: Okano T; Ishidou Y; Kato M; Imamura T; Yonemori K; Origuchi N; Matsunaga S; Yoshida H; tenDijke P; Sakou T (Reprint)
CORPORATE SOURCE: KAGOSHIMA UNIV, FAC MED, DEPT ORTHOPAED SURG, 8-35-1 SAKURAGAOKA, KAGOSHIMA 890, JAPAN (Reprint); KAGOSHIMA UNIV, FAC MED, DEPT ORTHOPAED SURG, KAGOSHIMA 890, JAPAN; KAGOSHIMA UNIV, FAC MED, DEPT PATHOL 1, KAGOSHIMA 890, JAPAN; JAPANESE FDN CANC RES, INST CANC, TOSHIMA KU, TOKYO 170, JAPAN; LUDWIG INST CANC RES, S-75124 UPPSALA, SWEDEN
COUNTRY OF AUTHOR: JAPAN; SWEDEN
SOURCE: JOURNAL OF ORTHOPAEDIC RESEARCH, (NOV 1997) Vol. 15, No. 6, pp. 820-829.
Publisher: JOURNAL BONE JOINT SURGERY INC, 20 PICKERING ST, NEEDHAM, MA 02192.
ISSN: 0736-0266.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Ossification of the posterior longitudinal ligament is a human genetic **disease** in which pathological ectopic ossification of the spinal ligaments develops. This leads to myelopathy or radiculopathy due to compression of the spinal cord. In this study, we investigated the histological features of orthotopic ossification of the spinal ligaments of senile Zucker fatty rats. A remarkably high incidence of orthotopic

ossification was observed mainly in the thoracic spinal ligaments as compared with controls The histopathological findings were similar to those for ossification of the human posterior longitudinal ligament. Bone morphogenetic proteins and activins, which exert their effects by way of specific type-I and type-II serine/threonine kinase receptors. play important roles in the formation of bone and cartilage. In the spinal ligaments of Zucker fatty rats, bone morphogenetic protein receptors and activin receptors were immunohistochemically **detected** around the ossified foci in a manner similar to that previously shown for the ossified **tissue** from patients who had ossification of the posterior longitudinal ligament. Thus, bone morphogenetic proteins and activin receptors might play important roles in orthotopic ossification of the spinal ligaments of Zucker fatty rats as well as in ossification of the posterior longitudinal ligament of humans. In addition, bone morphogenetic protein-receptor-IA was expressed in the nonossified ligament, suggesting that the spinal ligaments of the rats may have a predisposition to orthotopic ossification. In the controls, no expression of bone morphogenetic protein receptors or of activin receptors was observed. In conclusion, there is a great degree of similarity between orthotopic ossification of the spinal ligaments of Zucker fatty rats and ossification of the posterior longitudinal ligament of humans. Thus, the rats provide a useful animal model for the study of ossification of the human posterior longitudinal ligament.

L11 ANSWER 37 OF 41 EMBASE
on STN DUPLICATE 7

ACCESSION NUMBER: 96350577 EMBASE
DOCUMENT NUMBER: 1996350577
TITLE: Ectopic pulmonary ossification in human idiopathic pulmonary fibrosis and murine bleomycin-induced pulmonary fibrosis.
AUTHOR: Aoki K.; Saiki S.; Yoshimura K.
CORPORATE SOURCE: Department of Internal Medicine, Daisan Hospital II, Jikei University School of Medicine, 4-11-1, Izumi-Honcho,Komae, Tokyo 201, Japan
SOURCE: Jikeikai Medical Journal, (1996) 43/3 (191-205).
ISSN: 0021-6968 CODEN: JMEJAS
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
033 Orthopedic Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Ectopic ossification is often observed in the lung associated with diffuse fibrotic changes. To elucidate the pathogenesis of ectopic pulmonary ossification, morphological analysis was carried out in the human cases **diagnosed** as idiopathic pulmonary fibrosis (IPF) and in the murine pulmonary fibrosis model produced by the administration of bleomycin. Besides, expression of the genes for bone morphogenetic proteins (BMP-1, BMP-2, BMP-3, BMP-4, BMP-6, and **BMP-7**), the potential inducers of bone formation, was analyzed in the mouse lung using reverse transcription-polymerase chain reaction amplification. Evaluation of the serial sections of the human IPF lungs revealed mature forms of nodular or dendriform ossification located within the areas of intra-alveolar

granulation or fibrosis. Ectopic ossification was more frequently observed in the IPF cases complicated with severe congestive heart failure. In murine pulmonary fibrosis, mature nodular bone formation was also **detected** at 3 to 5 weeks after exposure to bleomycin, although immature form of ossification likely developed in quite a short period of time. Interestingly, expression of any BMP gene evaluated was not up-regulated in accordance with the progression of pulmonary fibrosis or ectopic bone formation, although constitutive BMP-2 mRNA expression was observed in the normal as well as bleomycin-treated mice. These data suggest that intra-alveolar exudation and its subsequent organization is likely the initial event in the process of pulmonary ossification, and delayed venous return associated with local **tissue** acidosis may play a crucial role for the osseous growth. However, BMPs are not likely to be directly involved in either ectopic ossification in the fibrotic lung **disease** or fibrosis per se.

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ACCESSION NUMBER: 95:614113 SCISEARCH
THE GENUINE ARTICLE: RT470
TITLE: RECOMBINANT BONE MORPHOGENETIC PROTEINS - NOVEL SUBSTANCES FOR ENHANCING BONE HEALING
AUTHOR: KIRKERHEAD C A (Reprint)
CORPORATE SOURCE: TUFTS UNIV, SCH VET MED, 200 WESTBORO RD, N GRAFTON, MA, 01536 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: VETERINARY SURGERY, (SEP/OCT 1995) Vol. 24, No. 5, pp. 408-419.
ISSN: 0161-3499.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: AGRI
LANGUAGE: ENGLISH
REFERENCE COUNT: 80

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Bone morphogenetic proteins (BMPs) are differentiative factors whose principal function is to induce transformation of undifferentiated mesenchymal cells into chondroblasts and osteoblasts in a dose-dependent manner. Bone morphogenetic proteins have been isolated postnatally in mammals from bone matrix, periosteal cells, mesenchymal cells of marrow stroma, tooth anlagen, and cells of osteosarcoma and chondrosarcoma. Distribution in additional embryonic **tissues** implies a broader organogenic function. Bone morphogenetic proteins are the only differentiative factors able to singularly induce de novo bone formation in vitro and in vivo. Recombinant DNA technology allows their production in large and highly purified **quantities**. The BMPs' osteoinductive ability has been shown with a variety of carriers including collagens and polymers at heterotopic and orthotopic sites in a wide range of species. They are presently being readied for clinical use as alternatives to bone grafts. Other potential applications include use as pulp capping agents, promoters of implant osteointegration and soft **tissue** reunion with bone, treatments for nonadaptive bone **disease**, and implants for use with mitotically expanded skeletal stem cell populations. Errors in the genetic coding of BMPs may manifest as clinical **disease** entities. (C) 1995 by The American College of Veterinary Surgeons

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on STN DUPLICATE 8

ACCESSION NUMBER: 95310771 EMBASE
DOCUMENT NUMBER: 1995310771
TITLE: A new biological approach to vital pulp therapy.
AUTHOR: Rutherford B.; Fitzgerald M.
CORPORATE SOURCE: Michigan Univ. School of Dentistry, 1011 N. University,Ann Arbor, MI 48109-1078, United States
SOURCE: Critical Reviews in Oral Biology and Medicine, (1995) 6/3 (218-229).
ISSN: 1045-4411 CODEN: CROMEF
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 011 Otorhinolaryngology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Molecular biology is providing opportunities to develop new strategies or agents for the treatment of a wide variety of **diseases**. The availability of large amounts of highly purified proteins produced by recombinant DNA techniques is an obvious example. Recent evidence has implicated proteins belonging to the bone morphogenetic protein (BMP) subgroup of the transforming growth factor beta supergene family in tooth formation and dentinogenesis. It has long been known that bone and dentin contain bone morphogenetic protein activity. Recently, recombinant human BMP-2, -4, and - 7 (also known as **OP-1**] have been shown to induce reparative dentin formation in experimental models of large direct pulp exposures in permanent teeth. The manner in which these agents act appears unique. New reparative dentin replaces the stimulating agents applied directly to the partially amputated pulp. Hence, the new **tissue** forms contiguous with, largely superficial to, and not at the expense of the remaining vital pulp **tissue**. This suggests a therapeutic approach permitting the induction of a **predetermined** and controlled amount of reparative dentin. Additionally, **OP-1** has been associated with the formation of reparative dentin after application to a freshly cut but intact layer of dentin. These findings may provide future clinicians with additional options for the treatment of substantially damaged or **diseased** vital teeth.

L11 ANSWER 40 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1994-065689 [08] WPIDS
CROSS REFERENCE: 1989-324202 [44]; 1989-324203 [44]; 1990-290311 [38]; 1991-148697 [20]; 1992-167101 [20]; 1992-167153 [20]; 1992-331475 [40]; 1993-100652 [12]; 1993-100993 [12]; 1993-117208 [14]; 1993-395405 [49]; 1994-007210 [01]; 1994-065304 [08]; 1994-065399 [08]; 1994-118107 [14]; 1994-118121 [14]; 1994-118146 [14]; 1994-118148 [14]; 1994-167392 [20]; 1994-302971 [37]; 1994-324521 [40]; 1996-010159 [01]; 1997-178399 [16]; 1997-384665 [35]; 1998-109345 [10]; 1998-158353 [14]; 1998-260496 [23]; 1998-333785 [30]; 1999-131303 [11]; 1999-589530 [50]; 2000-038265 [03]; 2000-422077 [36]; 2001-069971 [08]; 2002-415042 [44]; 2003-575998 [54]; 2003-584258 [55]; 2003-801273 [75]; 2004-008898 [01]; 2004-167144 [16]; 2004-374248 [35]
DOC. NO. NON-CPI: N1994-051387
DOC. NO. CPI: C1994-029529

TITLE: Morphogenic protein soluble complex - for regeneration of **tissue** in mammals and **diagnosing tissue disorders.**
DERWENT CLASS: B04 D16 S03
INVENTOR(S): COHEN, C M; KUBERASAMPATH, T; OPPERMANN, H; PANG, R H L; RUEGER, D C; JONES, W K; OZKAYNAK, E; TUCKER, R F
PATENT ASSIGNEE(S): (CREA-N) CREATIVE BIOMOLECULES INC
COUNTRY COUNT: 41
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9403600	A1	19940217	(199408)*	EN	120
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE					
W: AT AU BB BG BR CA CH CZ DE DK ES FI GB HU JP KP KR LK LU MG MN MW NL NO NZ PL PT RO RU SD SE SK UA					
EP 652953	A1	19950517	(199524)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
JP 07509611	W	19951026	(199551)		34
AU 678380	B	19970529	(199730)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9403600	A1	WO 1993-US7189	19930729
EP 652953	A1	EP 1993-918529	19930729
		WO 1993-US7189	19930729
JP 07509611	W	WO 1993-US7189	19930729
		JP 1994-505462	19930729
AU 678380	B	AU 1993-47951	19930729

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 652953	A1	Based on	WO 9403600
JP 07509611	W	Based on	WO 9403600
AU 678380	B	Previous Publ.	AU 9347951
		Based on	WO 9403600

PRIORITY APPLN. INFO: US 1993-40510 19930331; US 1992-923780 19920731; US 1993-29335 19930304
AN 1994-065689 [08] WPIDS
CR 1989-324202 [44]; 1989-324203 [44]; 1990-290311 [38]; 1991-148697 [20]; 1992-167101 [20]; 1992-167153 [20]; 1992-331475 [40]; 1993-100652 [12]; 1993-100993 [12]; 1993-117208 [14]; 1993-395405 [49]; 1994-007210 [01]; 1994-065304 [08]; 1994-065399 [08]; 1994-118107 [14]; 1994-118121 [14]; 1994-118146 [14]; 1994-118148 [14]; 1994-167392 [20]; 1994-302971 [37]; 1994-324521 [40]; 1996-010159 [01]; 1997-178399 [16]; 1997-384665 [35]; 1998-109345 [10]; 1998-158353 [14]; 1998-260496 [23]; 1998-333785 [30]; 1999-131303 [11]; 1999-589530 [50]; 2000-038265 [03]; 2000-422077 [36]; 2001-069971 [08]; 2002-415042 [44]; 2003-575998 [54]; 2003-584258 [55]; 2003-801273 [75]; 2004-008898 [01]; 2004-167144 [16]; 2004-374248 [35]
AB WO 9403600 A UPAB: 20040603

A dimeric protein (A) comprises a pair of protein subunits associated to give a structure with morphogenic activity. (A) has the following properties: (i) each subunit comprises at least 100 amino acids having a pattern of cysteine residues characteristic of the morphogen family; (ii) at least 1 subunit comprises a mature form of a subunit of a member of the morphogen family, or an allelic, species or sequence variant, noncovalently complexed with (iii)) a peptide comprising a pro-region of a morphogenic family member or allelic, species or sequence variant, to form a complex more solution in aqueous solvents than the uncomplexed subunits.

Also claimed are a method and a kit for **diagnosing** a **tissue disorder** or evaluating the efficacy of a therapy to regenerate lost or damaged **tissue** in a mammal.

Each subunit is pref. the mature form of human osteogenic protein (OP) **OP-1** and the pro-region peptide is the entire or partial sequence of the pro-region of **OP-1**.

Sequences of the N-terminal extensions of the mature forms of various suitable morphogens are given in the fig.

Antibodies that distinguish between soluble and mature forms of morphogenic proteins and method for producing these proteins and antibodies are disclosed.

USE/ADVANTAGE - The dimeric protein is useful in a therapeutic compsn. (claimed), pref. also containing a symptom-alleviating cofactor. The protein and corresp. antibodies may be used in **diagnostic** assays, e.g. to **quantitate** the amount of mature and soluble forms of morphogenic proteins produced in a body.

Dwg.2/2

L11 ANSWER 41 OF 41 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER:	1993-100993 [12] WPIDS
CROSS REFERENCE:	1989-324202 [44]; 1989-324203 [44]; 1990-290311 [38]; 1991-148697 [20]; 1992-167101 [20]; 1992-167153 [20]; 1992-331475 [40]; 1993-100652 [12]; 1993-117208 [14]; 1993-395405 [49]; 1994-007210 [01]; 1994-065304 [08]; 1994-065399 [08]; 1994-065689 [08]; 1994-118107 [14]; 1994-118121 [14]; 1994-118146 [14]; 1994-118148 [14]; 1994-167392 [20]; 1994-302971 [37]; 1994-324521 [40]; 1996-010159 [01]; 1997-178399 [16]; 1997-384665 [35]; 1998-109345 [10]; 1998-158353 [14]; 1998-260496 [23]; 1998-333785 [30]; 1999-131303 [11]; 1999-589530 [50]; 2000-038265 [03]; 2000-422077 [36]; 2001-069971 [08]; 2002-415042 [44]; 2003-575998 [54]; 2003-584258 [55]; 2003-801273 [75]; 2004-008898 [01]; 2004-167144 [16]; 2004-374248 [35]
DOC. NO. NON-CPI:	N1993-076814
DOC. NO. CPI:	C1993-044590
TITLE:	**Screening** cpds. to **determine** ability to modulate effective concentration of a morphogen - by assaying test tissue type cells for parameter indicative of a production level change of morphogen.
DERWENT CLASS:	B04 D16 S03
INVENTOR(S):	COHEN, C M; KUBERASAMPATH, T; OPPERMANN, H; OZKAYNAK, E; PANG, R H L; RUEGER, D C; SMART, J E; COHEN, C N; OZKAY-NAK, E
PATENT ASSIGNEE(S):	(CURI-N) CURIS INC; (CREA-N) CREATIVE BIOMOLECULES INC
COUNTRY COUNT:	19

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9305172	A1	19930318	(199312)*	EN	132
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL SE					
W: AU CA JP					
AU 9228624	A	19930405	(199330)		
EP 601129	A1	19940615	(199423)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE					
AU 678345	B	19970529	(199730)		
EP 1033574	A2	20000906	(200044)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE					
EP 601129	B1	20001115	(200059)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL SE					
DE 69231567	E	20001221	(200106)		
ES 2156862	T3	20010801	(200149)		
CA 2116560	C	20020108	(200206)	EN	

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9305172	A1		WO 1992-US7359	19920828
AU 9228624	A		AU 1992-28624	19920828
EP 601129	A1		EP 1992-921799	19920828
			WO 1992-US7359	19920828
AU 678345	B		AU 1992-28624	19920828
EP 1033574	A2	Div ex	EP 1992-921799	19920828
			EP 2000-100232	19920828
EP 601129	B1		EP 1992-921799	19920828
			WO 1992-US7359	19920828
		Related to	EP 1997-202681	19920828
		Related to	EP 2000-100232	19920828
DE 69231567	E		DE 1992-631567	19920828
			EP 1992-921799	19920828
			WO 1992-US7359	19920828
ES 2156862	T3		EP 1992-921799	19920828
CA 2116560	C		CA 1992-2116560	19920828
			WO 1992-US7359	19920828

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9228624	A	Based on	WO 9305172
EP 601129	A1	Based on	WO 9305172
AU 678345	B	Previous Publ.	AU 9228624
		Based on	WO 9305172
EP 1033574	A2	Div ex	EP 601129
EP 601129	B1	Related to	EP 1033574
		Related to	EP 825442
		Based on	WO 9305172
DE 69231567	E	Based on	EP 601129
		Based on	WO 9305172
ES 2156862	T3	Based on	EP 601129

Searcher : Shears 571-272-2528

CA 2116560 C Based on WO 9305172

PRIORITY APPLN. INFO: US 1991-752861 19910830
AN 1993-100993 [12] WPIDS
CR 1989-324202 [44]; 1989-324203 [44]; 1990-290311 [38]; 1991-148697 [20]; 1992-167101 [20]; 1992-167153 [20]; 1992-331475 [40]; 1993-100652 [12]; 1993-117208 [14]; 1993-395405 [49]; 1994-007210 [01]; 1994-065304 [08]; 1994-065399 [08]; 1994-065689 [08]; 1994-118107 [14]; 1994-118121 [14]; 1994-118146 [14]; 1994-118148 [14]; 1994-167392 [20]; 1994-302971 [37]; 1994-324521 [40]; 1996-010159 [01]; 1997-178399 [16]; 1997-384665 [35]; 1998-109345 [10]; 1998-158353 [14]; 1998-260496 [23]; 1998-333785 [30]; 1999-131303 [11]; 1999-589530 [50]; 2000-038265 [03]; 2000-422077 [36]; 2001-069971 [08]; 2002-415042 [44]; 2003-575998 [54]; 2003-584258 [55]; 2003-801273 [75]; 2004-008898 [01]; 2004-167144 [16]; 2004-374248 [35]
AB WO 9305172 A UPAB: 20040603

Screening candidate cpds. for the ability to modulate the effective concentration of a morphogen in an organism comprises incubating the cpd. with cells from a test tissue type known to produce a morphogen, for a time to allow the cpd. to affect morphogen production and assaying the cells for a parameter indicative of a change in the level of production of the morphogen.

Pref., the tissue type is human renal, kidney, bladder or adrenal-derived (**OP-1**) human nerve tissue derived, especially brain derived (GDF-1). Drosophila dorsal ectoderm, epithelial imaginal disc visceral mesoderm or gut endoderm tissue derived (DPP), mouse lung tissue (Vgr-1) or xenopus foetal endoderm tissue (Vg1)..

USE/ADVANTAGE - The method allows the **screening** of drugs for the ability to modulate the level in mammals of protein which can induce **tissue** morphogenesis, and allows the **determn.** of which animal **tissues** and/or cell types within a **tissue** express a partic. morphogenic protein. These cpds. may be used as drugs for human use, for increasing or decreasing morphogen production in vivo, to correct or alleviate a **disease** condition. Morphogens whose levels may be **determined** are especially **OP-1**, GDF-1, DPP, Vgr-1, or VGr, or may also be OP-2, 60A, CBMP2A, CBMP2B OR BMP 2, 3, 4, 5 or 6.

Dwg.1/3

(FILE 'MEDLINE' ENTERED AT 15:40:08 ON 17 DEC 2004)
L12 4532 SEA FILE=MEDLINE ABB=ON PLU=ON "BONE MORPHOGENETIC PROTEINS"/CT
L13 2971 SEA FILE=MEDLINE ABB=ON PLU=ON "CONNECTIVE TISSUE DISEASES"/CT
L14 0 SEA FILE=MEDLINE ABB=ON PLU=ON L12 AND L13

FILE 'HOME' ENTERED AT 15:41:35 ON 17 DEC 2004